The Journal of
CLINICAL ENDOCRINOLOGY
AND METABOLISM

VOLUME 14 JANUARY, 1954 NUMBER 1
Copyright 1954 by The Endocrine Society

HYPOTHALAMIC TUMOR AND PRECOCIOUS PUBERTY

T. P. MORLEY, F.R.C.S.*

The University Department of Neurosurgery, Royal Infirmary, Manchester, England

THE association of precocious sexual development with a tumor of the hypothalamus is so uncommon as to justify reporting this case.

Case No. 186080. R.G.C., a boy aged 7½, was admitted to the Neurosurgical Unit, Manchester Royal Infirmary on April 24, 1950, with headaches, vomiting and abnormal development of the external genitalia. Until six months before admission he had been a normal boy both mentally and physically. His first symptom was headache, often accompanied by vomiting which, with remissions lasting up to a few weeks, continued until shortly before admission. Three months after the onset of headaches his parents first noticed that his external genitals were growing abnormally large and pubic hair was appearing. At no time did the boy show any sexual desire and he was not observed to masturbate. He continued at school and did well there. Shortly after the onset of headache the boy himself observed a tremor of both hands which, however, was no embarrassment to his activities. He was well-mannered and quiet. His "physiologic" age was betrayed by a certain lack of that lawlessness which is common in boys of 8 or thereabouts, and by a distinct preference for adult rather than juvenile company. He would talk about "my girl friend" in an open, matter-of-fact way; she was a neighbor's daughter of his own age, towards whom improper advances had not been made, and the parents of both children regarded the relationship without disapproval.

Examination

He was a pleasant, intelligent boy who gave a clear account of his illness. He had a fair skin, ginger hair and brown eyes. His voice was broken but lapsed occasionally into

Received for publication May 29, 1953.

* Present address, Toronto General Hospital, Toronto, Ontario, Canada.

adolescent falsetto. The feet and hands were large and were in striking contrast to the rest of the body which was puny and stunted (Fig. 1). The thighs and legs were abnormally hairy for his age (but not for the degree of sexual development) and the growth

FIGURE 1

of pubic hair was well advanced (Fig. 2). Facial and axillary hair was not increased. The back was covered with a fine down. The external genitals were enlarged to the extent shown in the photograph (Fig. 2). The testes were of a size encountered normally in adolescence. Neurologic examination showed a moderate degree of bilateral papilloedema with some pallor of the discs, and the visual acuity was reduced to J.4 in each eye. The visual fields were full and the other cranial nerves functioned normally. All the limb reflexes were equal but abnormally brisk. The tremors of which the boy complained could be demonstrated easily and involved principally his arms, although on first waking or when suddenly confronted by an examiner, they spread to the trunk and started his whole body shaking slightly at a frequency of about three per second. When at rest and undisturbed he did not have a tremor.

Investigations

A roentgenogram of the skull showed widening of the sutures and erosion of the sella turcica, compatible with a chronic rise of intracranial pressure. A 24-hour specimen of urine showed the following: 17-ketosteroids, 4.2 mg. and 7.7 mg. (the normal for a boy

of 8 is up to 1 mg.); gonadotropins, 23 mouse units (M.U.) (normal 6–9 M.U.); no effect in the Aschheim-Zondek test or with 5 ml. of urine per mouse.

Diagnosis

A clinical diagnosis of third ventricle tumor was made. It was thought that the tumor was more likely to be a glioma of the third ventricle floor than a pinealoma, because there was no impairment of the movement of the eyes. There was no palpable adrenal or abdominal mass, and the intravenous pyelogram showed a normal calyceal pattern.

Progress

On June 8, 1950, an air ventriculogram under local anesthesia showed symmetrical dilatation of both lateral ventricles, with complete absence of air in the third ventricle.

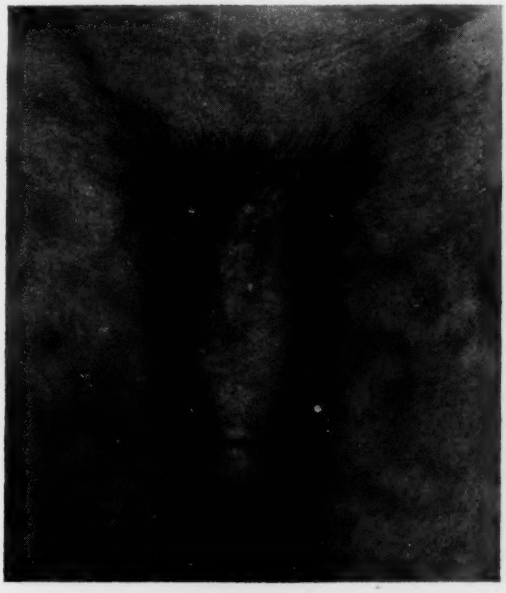


FIGURE 2

No air escaped into the subarachnoid space. Ventricular cerebrospinal fluid (C.S.F.) contained 25 mg. of protein per 100 ml. During the time between admission and the taking of ventriculograms the boy had been nearly free from headache, and the papilloedema had receded. He was active around the ward and the tremors had almost vanished. On June 12, 1950, he was discharged. He returned to school and caught up in class with the others of his age. His vision had returned to J.1 in each eye and the optic discs had been flat. In other respects his behavior had been unchanged.

Over a year later he was re-admitted (August 27, 1951) when it was plain that increased intracranial pressure had returned. He was much less lively than before, and content to lie quietly in bed all day. During the few months before this second admission he had had occasional headaches, culminating in a severe series in August while at sea

on a trawler with his father. Little increase in height had taken place during the year at home, but the genitals had developed further. The only other change of note was that the tremors were more pronounced. Papilloedema was present again; the visual fields remained full. On August 30, 1951, a bilateral ventriculocisternostomy (Torkildsen) was performed. The cerebrospinal fluid from each lateral ventricle contained 10 mg. of protein per 100 ml. Six weeks later he died. He had shown all the signs and behavior of a patient with postoperative meningitis, yet no organism could be isolated from the C.S.F. Intensive chemotherapy and the use of antibiotics failed to bring the infection under control, as judged by the C.S.F. analysis. The situation and the size of the tumor were undoubtedly the cause of his death. Although he remained conscious, the tremors became much more severe. Later, he became blind in the left eye and this was followed shortly before death by a left hemiplegia.

While under observation as both an in-patient and out-patient, he did not exhibit other signs of hypothalamic depression or overactivity. His sleep requirement and rhythm were normal, and his appetite was normal. There was neither polydipsia nor polyuria. Temperature, pulse, respiration and blood pressure were invariably (except during his last illness) within the normal range.

Postmortem examination

A full examination was made, but apart from the wasting due to his final illness and the abnormalities of development already mentioned, the brain was the only site of disease. There was no gross evidence of subarachnoid infection or of ventriculitis. The adrenals were normal to the naked eye and microscopically. The pituitary body showed no gross abnormality.

Brain: The presence of a large internal hydrocephalus was confirmed. The third ventricle was completely occupied by a tumor measuring 5×4×4 cm. (Figs. 3 and 4). The boundaries of the spherical tumor were well demarcated from surrounding brain; in fact, when cuts were made across the tumor in several directions it fell out of its bed, except at its point of attachment in the region of the third ventricle floor. The optic chiasm was grossly attenuated and the optic tracts too were considerably stretched round the tumor; the chiasm was incorporated in the capsule. The attachment of the pituitary stalk was clearly identified and the lamina terminalis, the fornix, the pineal and mammillary bodies could all be seen as structures separate from the tumor, although the last were greatly compressed and diminished in size. The cavity of the third ventricle existed only as a potential space between the superior surface of the tumor and the roof of the ventricle. The third and fourth cranial nerves were not incorporated in the growth or its capsule. The cut surface of the tumor showed an inferior half that was red and fleshy with many tiny cysts and one larger cyst; the upper half was pale and more homogeneous.

Histology: (Dr. Kathleen V. Lodge). Section shows a typical astrocytoma composed of well differentiated stellate cells. Some areas show edema, whereas in others there is a microcystic appearance. There are occasional areas showing a "piloid" pattern, with conspicuously fibrillary elongated cells. The neoplasm is everywhere well differentiated and shows no evidence of rapid growth. There is fairly clear demarcation between tumor and surrounding brain tissue, with no definite invasion (Fig. 5). Sections of the testis (Fig. 6) show seminiferous tubules, the majority of which have a definite lumen. Spermatocytes are numerous and their nuclei show fine darkly staining chromatin granules. A

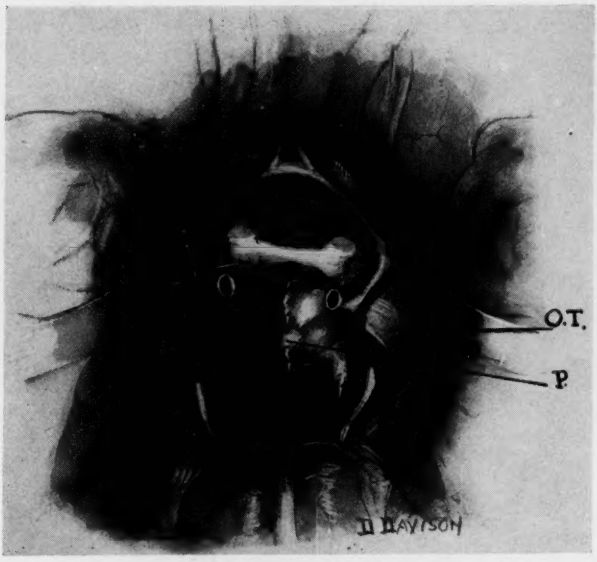


FIG. 3. Appearance of tumor from below, before section. O.T. = Optic tract. P. = Attachment of pituitary stalk.

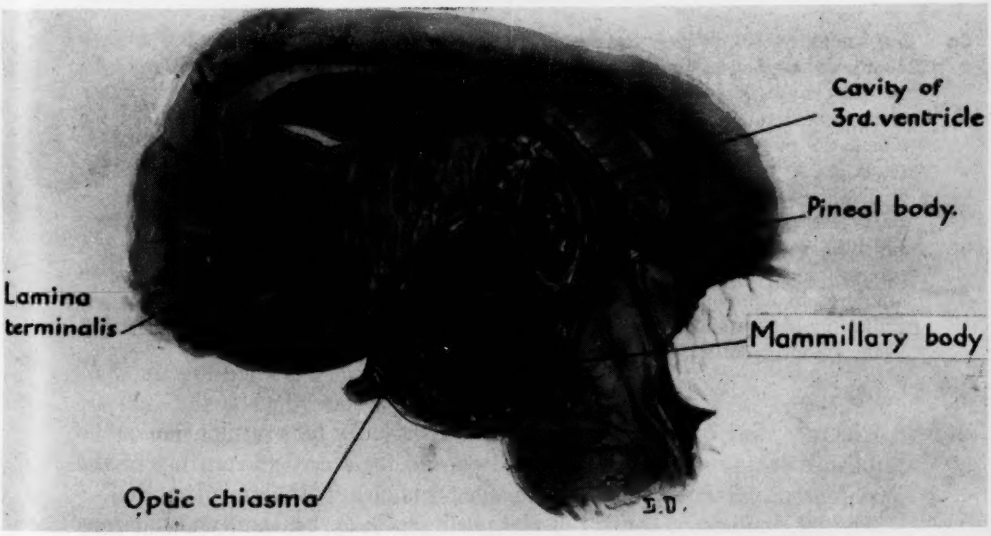


FIG. 4. Sagittal section through tumor and region of third ventricle.

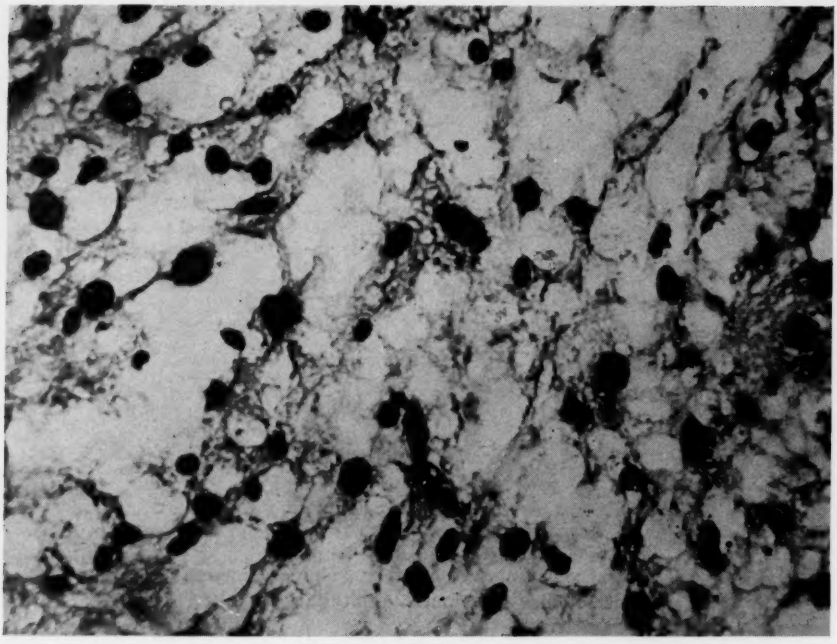


FIG. 5. Astrocytoma of hypothalamus. (Hematoxylin and eosin, ×315.)

large number of mitotic figures are present in the spermatocytes. Spermatids are less numerous but they are present in normal proportions in some of the tubules. A few of the tubules contain occasional well formed spermatozoa. Interstitial cells are present in the testis in moderate numbers. These findings indicate that the testis has been under the stimulation of gonadotropic hormone and that the changes associated with puberty have taken place.

The prostate consists of a fibromuscular stroma in which there are numerous prostatic gland acini. Most of the acini are tortuous and lined by a single layer of epithelium which is largely of columnar type, though in some acini flattened. The presence of a columnar epithelial lining in the acini suggests that the prostate is under the stimulation of androgenic hormone (Ham (1)). The adrenal gland shows no abnormality and, when stained by Broster and Vines' technique, no fuschinophilic material can be demonstrated in the cytoplasm of the cells.

DISCUSSION

The recording of this case affords an opportunity for examination of the published facts regarding this condition and for a critical scrutiny of the hypotheses and theories behind some aspects of hypothalamic function.

The mechanism of control of the pituitary body by the hypothalamus may be summarized. The neurohypophysis (posterior lobe) is under the nervous control of the hypothalamus through the supraoptico-hypophyseal

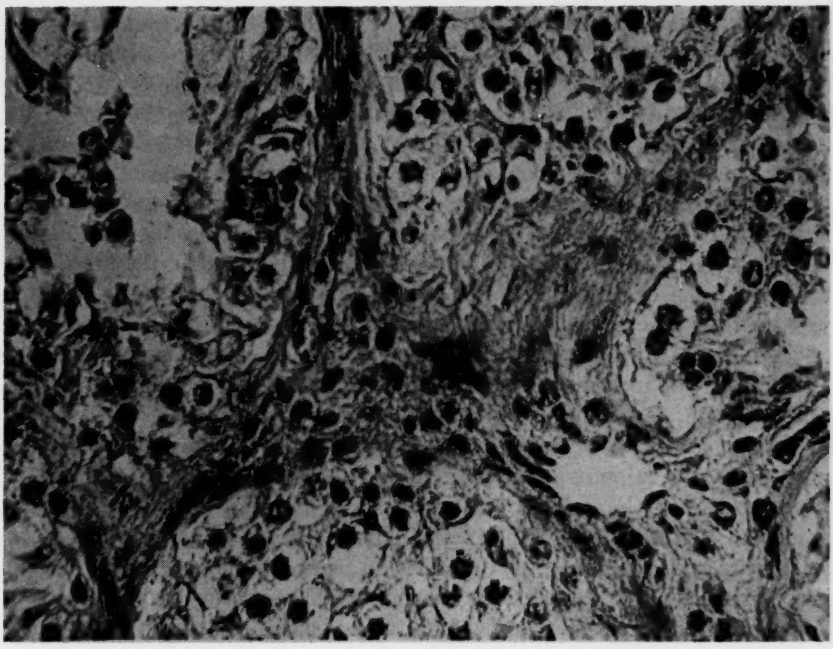


FIG. 6. Testis. (Hematoxylin and eosin, ×165.)

tract. Experimentally, secretory activity of the posterior lobe follows emotional stress and increase in the tonicity of the blood. The adenohypophysis (anterior lobe) has direct neural connections with the cervical sympathetic, the parasympathetic and the hypothalamus, but section of these pathways is compatible with normal function of the gland. More important is the venous portal supply to the adenohypophysis, from the pars tuberalis and adjacent tuber cinereum. It has been demonstrated by Harris (2) that stimulation of this region in the rabbit results in gonadotropic secretion when the only connection between the hypothalamus and pituitary is the portal system. It is still not known what in its turn stimulates the hypothalamus, nor even whether the stimulus is purely neurogenic from "higher" centers in the brain, or chemical, borne from distant parts of the body by the blood stream.

Various features of the disorder, noted in this and previously reported cases, warrant separate consideration.

a) *Site of lesion.* This paper is concerned only with intracranial lesions and not with those other conditions (*e.g.*, adrenocortical and gonadal tumors) that give rise to pubertas praecox. Krabbé (3) held that although less than 10 per cent of pineal tumors in children give rise to sexual

precocity, in those cases in which the syndrome is present, the tumor responsible is a teratoma. Although other authors have shown that pinealomas and a variety of other neoplasms can cause sexual precocity, the fact that pineal tumors seldom do so may be ascribed to a peculiarity in the anatomy of their development. Reference to the illustrated reports of pineal tumors that have come to postmortem examination and to those from this department, show that the almost invariable tendency of these lesions is to enlarge backwards by growing out beneath the tentorium. By compressing the tectum and cerebellum they give rise in the first place to disorders of eye movements and to obstruction of the iter. It is noteworthy that pineal tumors so seldom grow forwards into the third ventricle and on to the hypothalamus; if they did so, associated sexual precocity might be more common. In all other instances of precocity of intracranial origin, the lesion is in the floor of the third ventricle (Seckel *et al.* (4), Papez and Ecker (5), Weinberger and Grant (6)). In many cases the posterior hypothalamus is chiefly involved and this is to be expected when a pineal tumor is the cause. A tumor in this situation, however, is not always associated with gonadal hyperplasia. Thus, although nearly all cases of sexual precocity of intracranial origin can be shown to be due to a lesion involving the hypothalamus, by no means all lesions in this region give rise to pubertas praecox. The size of a tumor bears no relation to its effect.

b) *The nature of the lesion.* The pineal teratoma, to the exclusion of the pinealoma, has by some been held to predispose particularly to sexual precocity (Krabbé). There seems to be little correlation, however, between the clinical syndrome and any one pathologic disorder. The site of the lesion is far more consistent than the nature of it. Of the pineal tumors it is true that teratomas are more commonly encountered in sexual precocity than are pinealomas, but the latter also have been found responsible. Apart from such a case admitted to this department (#232/42, K.B., a boy, aged 9), that described by Horrax and Bailey (7) is of special interest. At postmortem examination a pinealoma was found but there was also in the floor of the third ventricle another tumor of considerable size which was proved on microscopic examination to be pinealoma as well. It would seem that the site of this tumor was the important fact, rather than its nature. Sixteen primary hypothalamic tumors have been reported, including astrocytoma, infundibuloma, neurofibroma, and hamartoma or ganglioneuroma. This very diversity suggests that the pathologic type is not of great importance; moreover, the responsible tumor cannot be secretory, when its type is neurofibroma or astrocytoma. (For tabulation of reported cases see Weinberger and Grant's paper (6).)

c) *Hormone assay.* The opportunity has seldom arisen in the past for hormone estimations to be carried out in this type of case. Wilkins (8),

however, reports a case similar to the one described in this paper. The patient was a boy of 4 years, with enlarged penis and testes. Urinary 17-ketosteroid excretion was moderately increased, and the gonadotropin level was within the normal adult range. Wilkins (9) states that precocity of adrenal origin can be distinguished from that of intracranial and 'idiopathic' origin if the visible signs of abnormal development and the 17-ketosteroid excretion are known. Thus in idiopathic and intracranial precocity the development of the penis and testes is excessive, the bodily contours are adolescent in appearance and the 17-ketosteroid excretion is at adolescent or adult levels but not above. These findings were encountered in the boy described here. In precocity of adrenal origin, however, the testes are immature and the 17-ketosteroid excretion is greatly in excess of that in the adult.

d) *Sexual behavior and mental development.* From these two aspects there could hardly be greater variation in the observations. The boy of Le Marquand's report (10) whose restlessness and bestiality could not be curbed, the plump child with mental and physical lethargy, and the patient reported here (an intelligent, self-effacing boy, undisturbed by libido) all illustrate the wide differences in physiologic manifestation that may be encountered in this condition.

e) *The varieties of clinical syndromes* caused by a hypothalamic lesion must be referred to. One, several, or all of the hypothalamic functions may be deranged by any type of lesion. It was remarkable that in our patient temperature control, water, carbohydrate and fat metabolism and the rhythm of sleep showed no variation from the normal; thus, although the tumor had apparently destroyed the whole hypothalamus, it had upset only one of its functions. Papez and Ecker (5) in their case made a microscopic analysis of the cell groups remaining in the hypothalamus surrounding the tumor, and attempted to assess the percentage injury to the different nuclei. Important as the charting of the undamaged area may be in an investigation of this condition, it is unjustifiable to attribute a function or lack of function to the presence of a lesion in one part of the hypothalamus or its absence in another. (It should be said that Papez and Ecker made no such interpretation; they simply recorded their observations.)

f) *Mechanism.* This case demonstrates well how a tumor in a 'vital' center is compatible with almost normal function, provided its rate of growth is slow. Operative damage of far less extent in the same region is fatal.

How, then, does a hypothalamic tumor cause pubertas praecox? 1) The view put forward by Clark *et al.* (11), Weinberger and Grant (6), and subscribed by Papez and Ecker (5) is that lesions of the hypothala-

mus, particularly in its posterior part, release the adenohypophysis from the inhibitory control of the hypothalamus. However, such 'inhibition' of the anterior pituitary has never been demonstrated. From experimental evidence, hypothalamic destruction would be expected to result in depression of sexual and other pituitary manifestations. This is often the case in tumors that grow in this region in adults. It is still true, as it was in 1941 (Weinberger and Grant), that no experimental ablative lesion of the brain has produced enhanced sexual function. 2) Although in the present case a hormone assay of the tumor removed at autopsy was not performed, it is improbable that it was elaborating gonadotropins, especially as other histologic types of tumor have been found associated with the same precocity. It is hardly credible that astrocytoma, infundibuloma, or neurofibroma could secrete; and, even if they did, that the same hormone should come from each. 3) Some authors have held that the anterior pituitary is overactive in the presence of increased intracranial pressure, but Henderson and Rowlands (12) were unable to confirm this observation. Moreover, tumors of the hypothalamus cannot give rise to hydrocephalus until the disease is well advanced.

It appears, therefore, that in pubertas praecox of intracranial origin the lesion must be situated in the hypothalamus. Furthermore, the published cases show that the pathologic nature of the lesion is of no consequence, nor is its size. Although the hypothesis of the anterior pituitary being released from hypothalamic inhibition is rejected, the proposition that the tumor itself stimulates the hypothalamus should at least be examined. This suggestion is not so heretical as it first seems, for it has long been accepted that, in the brain, neurologically inert tissue can excite the brain as a whole and produce a sequence of nervous impulses. Obvious examples of this are the epileptogenic properties of cerebral scarring or of tumors that do not contain active neural tissue. However, perhaps a more satisfying explanation (particularly when the hypothalamus is destroyed) is that other parts of the brain, or even of the body, take over the function of the diseased or destroyed hypothalamus. It may be naïve to suggest that other nervous centers accept the duties of the hypothalamus on default, and perhaps attention should be directed away from the nervous system. It is not impossible that adrenocortical hormone can under abnormal circumstances be converted to androgens outside the adrenal gland itself (13); therefore, it seems no less likely that the hormonal substance which is (in the intact brain) elaborated by the hypothalamus and carried by way of the blood to the adenohypophysis can, in disease of the hypothalamus, be produced excessively elsewhere in the body. This conjecture, although conforming to modern views on the body's reaction to stress, does not dispose of many

difficulties. There is no disputing the diverse experimental and clinical findings: a) that no experimental destructive lesion in the brain has ever been productive of sexual precocity; b) that tumors in identical situation may give rise to very different clinical syndromes; c) that anatomic and physiologic studies appear to demonstrate areas in the hypothalamus subserving different functions—an observation which clinical investigations cannot always support; and d) that some lesions in the floor of the third ventricle depress, whereas other apparently similar ones enhance hypothalamic and pituitary functions. When the facts lead to conflicting theories, it is the interpretation that is wrong; somehow, a reconciliation must be found.

SUMMARY

1. A case of pubertas praecox associated with astrocytoma of the hypothalamus is recorded.

2. The subject is reviewed with reference to previously published cases, in an attempt to clarify the relationship between tumor and increased gonadotropic hormone activity.

3. It is suggested that, in the presence of disease or destruction by tumor of the hypothalamus, the hormones normally elaborated there may be produced elsewhere in the brain or body.

Acknowledgments

This case was admitted to the hospital under the care of Sir Geoffrey Jefferson, F.R.S., to whom I am indebted for permission to publish and for criticism.

Miss D. Davison's pictures are gratefully acknowledged.

REFERENCES

1. Ham, A. W.: Histology. Philadelphia, J. B. Lippincott Co., 1950, p. 664.
2. Harris, G. W.: Neural control of the pituitary gland. II. The adenohypophysis, *Brit. M. J.* **2**: 627 (Sept. 15) 1951.
3. Krabbé, K. H.: Un cas de tératome dans la glande pinéale, gueri per intervention opératoire, *Acta psychiat. et neurol.* **19**: 233, 1944.
4. Seckel, H. P. G.; Scott, W. W., and Benditt, E. P.: Six examples of precocious sexual development; studies in diagnosis and pathogenesis, *Am. J. Dis. Child.* **78**: 484 (Oct.) 1949.
5. Papez, J. W., and Ecker, A.: Precocious puberty with hypothalamic tumor (infundibuloma); case report, *J. Neuropath. & Exper. Neurol.* **6**: 15 (Jan.) 1947.
6. Weinberger, L. M., and Grant, F. C.: Precocious puberty and tumor of hypothalamus; report of case and review of literature, with patho-physiologic explanation of precocious sexual syndrome, *Arch. Int. Med.* **67**: 762 (Apr.) 1941.
7. Horrax, G., and Bailey, P.: Tumors of the pineal body, *Arch. Neurol. & Psychiat.* **13**: 423 (Apr.) 1925.
8. Wilkins, L.: The Diagnosis and Treatment of Endocrine Disorders in Childhood

and Adolescence. Springfield, Ill., Charles C Thomas, Publisher, 1950, chapter 10, p. 164.

9. WILKINS, L.: The diagnosis of the adrenogenital syndrome and its treatment with cortisone, *J. Pediat.* **41:** 860 (Dec.) 1952.
10. LEMARQUAND, H. S.: Case of pubertas praecox (macrogenitosomia praecox) in boy associated with tumour in floor of third ventricle, *Roy. Berkshire Hosp. Rep.* pp. 31–61, 1934–35.
11. CLARK, W. E. L.; BEATTIE, J.; RIDDOCH, G., and DOTT, N. M.: The Hypothalamus: Morphological, Functional, Clinical and Surgical Aspects. Edinburgh, Oliver & Boyd, 1938, p. 184.
12. HENDERSON, W. R., and ROWLANDS, I. W.: The gonadotrophic activity of the anterior pituitary gland in relation to intracranial pressure, *Brit. M. J.* **1:** 1094 (May 21) 1938.
13. SAYERS, G.: Adrenal cortex and homeostasis, *Physiol. Rev.* **30:** 241 (July) 1950.

ENDOCRINE AND OTHER CLINICAL MANIFESTATIONS OF HYPOTHALAMIC DISEASE

A SURVEY OF 60 CASES, WITH AUTOPSIES*

HANS G. BAUER, M.D.†

The New York Medical College, Metropolitan Hospital Research Unit, Welfare Island, New York, N. Y.‡

INTRODUCTION

RESEARCH on the hypothalamus of animals has given us a wealth of information regarding alteration of function, obtained by producing pinpoint lesions in this autonomic center. Such lesions are made with stereotaxic instruments. In the study of human disease, however, we very seldom see such selective lesions. Any pathologic condition involving the hypothalamus usually affects at least one third, if not two thirds of this organ. This is not surprising when one considers the following facts: The whole hypothalamus weighs approximately 4 grams (the size of the terminal phalanx of a grown man's thumb). This small area contains about 15 to 20 paired nuclear centers, of which the afferent and efferent nerve fibers likewise have to run through this narrow region. The clinical observer therefore will usually be confronted with a rather complex situation as far as symptomatology is concerned.

It was felt that a survey of a fairly large number of cases with various pathologic lesions of the hypothalamus might emphasize some common clinical points which would guide the clinician to make an early diagnosis, thus enabling him to institute a systematic neurologic investigation before the more obvious neurologic and neuro-ophthalmogic signs appear.

CASE MATERIAL

Sixty cases with various lesions in the hypothalamus have been collected from the literature (1–36). Autopsies were performed in all (Table 1). The sex distribution was 40 males and 20 females. The hypothalamic pathology consisted of 51 neoplasms, 7 inflammatory lesions and 2 degenerative ones (Table 2).

Received for publication June 6, 1953.

* Presented at the Annual Meeting of the Endocrine Society, New York, N. Y., May 28–30, 1953.

† Address: 47 East 61st Street.

‡ Dr. Thomas H. McGavack, Director.

TABLE 1. SHORT DESCRIPTION OF CASES

Case No. and author	Lit. ref.	Patient's age & sex	Diagnosis	Portion of hypothalamus involved	Predominant clinical features
1. Schmalz	(1)	12 M	Neurofibroma	Floor 3rd ventricle, tuber cin., corp. mammill.	Precoc. puberty, psych. disturb., pyram., cerebell. & eye signs
2. Gross	(2)	2 F	Astrocytic hamartoma	Floor 3rd ventricle, corp. mammill.	Precoc. puberty, oliguria, obesity, pigment'n.
3. Gross	(2)	7 M	Ganglioneuroma	Floor 3rd ventricle, stalk of pituitary (for. Monro blocked)	Precoc. puberty, obesity, diab. insip., dyshidr.
4. Papez *et al.*	(3)	8 M	Infundibuloma	Floor 3rd ventricle, corp. mammill. flatten'd, tuber cin. partly	Precoc. puberty, psych. disturb anorexia, cerebell. signs, emac.
5. Bailey *et al.*	(4)	9 M	Pilocytic astrocytoma	Third ventricle obliterated	Precoc. puberty, convuls., cerebell. signs
6. Vickers *et al.*	(5)	8 M	Astrocytoma	Tuber cin.; corp. mammill. obliterated	Precoc. puberty, fits of rage
7. Saar	(6)	4 M	Glioma	Corp. mammill.; 3rd ventricle filled	Precoc. puberty, emac., psych. disturbs.
8. Horrax *et al.*	(7)	7 M	Ganglioneuroma	Third ventricle, attached to infundib.	Precoc. puberty, eye signs, obesity, diab. insip.
9. Heuyer *et al.*	(8)	6 M	Ependymoma	Corp. mammill., resting on subst. perforata	Precoc. puberty, violent reactions, cerebell. signs, meningism
10. Clark *et al.*	(9)	8 F	Astrocytoma	Floor 3rd ventricle, post. tuber cin. to post. margin of corp. mammill.	Precoc. puberty, decerebr. rigidity with aura of laughing
11. Poston *et al.*	(10)	2 M	Astrocytoma	Arising from left corp. mammill.	Precoc. puberty, psych. disturbs., incont., convuls., cerebell. signs, cyanosis
12. DeLange	(11)	10 M	Astrocytoma	Infundib. up to thalamus; corp. mammill. preserved	Precoc. puberty, psych. disturbs., neurol. signs (pyram., cerebell., eye)
13. Clement	(12)	7 M	Astrocytoma	Post. hypothalamus	Precoc. puberty, oliguria, hypertension
14. Seckel *et al.*	(13)	5 F	Hyperplastic malformation	Arising from tuber cin., attached to pons, beneath rt. corp. mammill.	Precoc. puberty
15. Spatz	(14)	2 M	Hyperplastic malformation	Behind infundib., covering corp. mammill.; no pressure	Precoc. puberty
16. LeMarquand	(15)	2 M	Hyperplastic malformation	Attached to tuber cin. and rt. corp. mammill.	Precoc. puberty, pyram. & cerebell. signs, dysthermia, bulimia
17. Bronstein	(16)	2 M	Hyperplastic malformation	Post. tuber cin.; no hypothalamic damage	Precoc. puberty, oliguria, hypertension
18. Tannhauser	(17)	¼ F	Congenital malformation	Third ventricle, subthalamic area	Precoc. puberty
19. Horrax *et al.*	(18)	12 M	Pinealoma, metast. implant 3rd ventr.	Tumor implant on floor of 3rd ventricle	Precoc. puberty, dysthermia, diab. insip., eye & cerebell. signs, convuls.
20. Hellner	(19)	12 M	Encephalitic TBC	Periventricular	Precoc. puberty, diab. insip., eye signs
21. Thomas *et al.*	(20)	12 M	Encephalomeningitis	Pachymeningitis cervical region, with blocking of arachn.-ventr.	Precoc. puberty, meningitis signs
22. Poos	(21)	12 M	Encephalitis	Periventricular	Precoc. puberty, diab. insip., eye & pyram. signs
23. Saar	(6)	7 M	Meningoencephalitis	Periventricular	Precoc. puberty, diab. insip., eye signs
24. Krabbé	(22)	1 M	Tuberous sclerosis	Corp. mammill.	Precoc. puberty, convuls., dyshidr.
25. Collins	(23)	28 F	Craniopharyngioma	All hypothalamic nuclei destroyed	Hypogonadism, psych. disturbs. somnol., obesity, diab. insip., vasomot. disturb., dysthermia
26. Globus *et al.*	(24)	3 M	Craniopharyngioma	Adherent to walls of 3rd ventricle, sella turcica	Hypogonadism, somnol., diab. insip., dysthermia, pyram. & eye, signs
27. Globus *et al.*	(24)	10 M	Craniopharyngioma	Optic chiasm to pons, floor 3rd ventricle att. to pituitary	Hypogonadism, eye signs, obesity

TABLE 1—(*continued*)

Case No. and author	Lit. ref.	Patient's age and sex	Diagnosis	Portion of hypothalamus involved	Predominant clinical features
28. Globus *et al.*	(24)	15 M	Craniopharyngioma	Floor, walls 3rd ventricle, infundib.	Hypogonadism, retarded growth, somnol., dysthermia
29. Globus *et al.*	(24)	25 F	Craniopharyngioma	From base of brain, ant. hypothalamus to cerebral peduncles	Hypogonadism, amenorr., emac., diab. insip., somnol., eye signs
30. Globus *et al.*	(24)	33 F	Craniopharyngioma	Third ventricle filled out	Hypogonadism, amenorr., eye signs, somnol., diab. insip., dysthermia
31. Globus *et al.*	(24)	42 M	Craniopharyngioma	From beneath optic chiasm, filling 3rd ventricle	Hypogonadism, eye signs, diab. insip.
32. Davison	(25)	45 F	Craniopharyngioma	From lower ant. hypothalamus into 3rd ventricle; corp. mammill. spared	Hypogonadism, early menop., eye signs, obesity, psych. disturb., dysthermia
33. Globus	(26)	13 M	Infundibuloma	Floor 3rd ventricle, depressing diaphragm of sella	Hypogonadism, dysthermia, emac.
34. Globus	(26)	5 F	Infundibuloma	Origin 3rd ventricle, base of brain	Hypogonadism, headaches, vomiting, cerebell. signs
35. Clark *et al.*	(9)	37 M	Cyst in infundibulum	Through floor of 3rd ventricle, tuber cin.	Hypogonadism, emac., somnol., pyram. signs
36. Cleghorn	(27)	23 M	Pinealoma	Floor 3rd ventricle, aqueduct obstructed, edema lt. hypothalamus	Hypogonadism, somnol., emac., psych. disturb., bulimia, urin. incont.
37. Bailey *et al.*	(28)	15 M	Pinealoma	Filling 3rd ventricle, 15-mm. nodule of tumor around stalk	Hypogonadism, diab. insip., dysthermia, emac., psych. disturb., eye signs, obesity
38. Davison	(25)	10 M	Unidentified tumor	Filling 3rd ventricle, obstr. of aqueduct with int., hydroceph.	Hypogonadism, eye and pyram. signs, psych. disturb., obesity, dysthermia
39. Bailey *et al.*	(28)	28 F	Peritheloid sarcoma	Tuber cin., floor 3rd ventricle, infundibulum	Hypogonadism, somnol., diab. insip., obesity, eye signs
40. Davison	(25)	31 M	Angioma	All nuclei of infundib. destroyed	Hypogonadism, eye signs, diab. insip., obesity, somnol., dyshidr., dysthermia
41. Anderson	(29)	30 M	Meningoencephalitis	Scar band median eminence nucleus periventric. arcuatus	Hypogonadism, retarded growth, obesity, eye signs, dyshidr.
42. Ayala	(30)	17 M	Meningoencephalitis	Tuber cin., periventric.	Hypogonadism, eye, cerebell. & pyram. signs, obesity, incont., psych. disturb., dysthermia
43. Moore *et al.*	(31)	M	Encephalitis	Periventric. infilt.	Hypogonadism, diab. insip., emac., obesity, eye signs
44. Fine	(32)	6 M	Infundibuloma	Almost complete replacement of hypothalamus	Eye signs, vomiting, headaches, psych. disturb.
45. French	(33)	F	Plasmo-cystoma	Mass occupying all of hypothalamus, olfact. nerve, pineal	Headaches, somnol., psych. disturb., dysthermia, irreg. menses
46. Globus *et al.*	(24)	6 F	Craniopharyngioma	Tuber cin., corp. mammill.	Bulimia, diab. insip., headaches, fatigability, pyram. signs
47. Globus *et al.*	(24)	15 F	Craniopharyngioma	Over sella, interpedunc. space to cerebello-pontine angle	Emac., then obesity, diab. insip., eye signs, somnol., convuls., incont.
48. Globus *et al.*	(24)	7 F	Craniopharyngioma	Lat. walls of 3rd ventricle	Headaches, vomiting, emac., eye signs, psych. disturb.
49. Globus *et al.*	(24)	50 F	Craniopharyngioma	Large mass, adherent to occip. bone base, below lt. temp. lobe	Eye signs, vomiting, headaches, dysphagia, emac., cerebell. signs
50. Globus *et al.*	(24)	10 M	Craniopharyngioma	Entering 3rd ventricle, partly on its floor	Eye signs, lethargy, decerebr. rigidity, pyram. signs, convuls.
51. Globus *et al.*	(24)	21 M	Craniopharyngioma	Base of brain, floor 3rd ventricle tuber cin., corp. mammill.	Headaches, convuls., eye signs, psych. disturb., pyram. signs
52. Globus *et al.*	(24)	54 M	Craniopharyngioma	Optic chiasm to interpedunc. space into thalamus	Somnolence, obesity, headaches, eye signs

TABLE 1—(*continued*)

Case No. and author	Lit. ref.	Patient's age and sex	Diagnosis	Portion of hypothalamus involved	Predominant clinical features
53. Thomas *et al.*	(34)	10 M	Medulloblastoma	Extensive involv. of hypothalamus. Only subst. grisea spared	Headaches, vomiting, cerebell. and pyram. signs
54. Draganesco *et al.*	(35)	63 F	Ependymoma	Nuclei of tuber cin. severely damaged	Psych. disturb., somnol., obesity, diab. insip.
55. Davison	(25)	52 M	Unidentified; 5 cm. diameter	Invasion and compress. of hypothalamus, corpus luysi; corp. mammill. invaded	Somnol., obesity, dysthermia, pyram. signs, psych. disturb.
56. Bailey *et al.*	(28)	38 M	Cyst of choroid plexus	Attached to roof of hypothalamus; small nodule at stalk	Vertigo, headaches, eye signs, vomiting, psych. disturb., somnol.
57. Davison	(25)	31 M	Lt. frontal lobe tumor	Metast. to 3rd ventricle, infundib., corp. mamill., med. walls 3rd ventricle	Cerebell. & eye signs, convuls., emac., dysthermia
58. Davison	(25)	23 F	Soft, pearly tumor	Lt. post. wall 3rd ventricle, obstr. aqued., corp. mammill.	Dysthermia, hirsutism, vertigo, psych. disturb., pyram. signs
59. Sunderman	(36)	F ½	Hemangioendothelioma, malig.	Post. walls 3rd ventricle, ventrodorsal & medial nucleus	Dysthermia, diuresis, somnol., elevat. serum magnes., low calcium
60. Davison	(25)	67 F	Arteriosclerotic degen. change	Caudal hypothalamus	Dysthermia

CLINICAL OBSERVATIONS

Degree of involvement of hypothalamus and number of symptoms

By dividing the hypothalamus roughly into anterior, posterior and inferior (tubero-infundibular) thirds, it was found that among 52 cases 6 showed destruction of the entire hypothalamus, 35 showed destruction of between one third and two thirds, and only 11 showed destruction of less than one third. The extent of involvement, however, did not necessarily correspond to the degree of function lost or altered. One of the 6 cases with total destruction of the hypothalamus showed only strictly neurologic disorders and no hypothalamic signs. In another subject with no functioning hypothalamic tissue left, only one vegetative function was affected; in 2 other instances, eight and six functions, respectively, were modified. On the other hand, 1 case with very small lesions displayed alteration of six hypothalamic functions. The average number of hypothalamic-linked symptoms was three per case.

Lesions of the floor of the third ventricle give rise to more symptomatology than lesions in the walls or the roof of this ventricle. Among 22 cases with lesions in the floor of the third ventricle the highest number of associated symptoms was eight in 1 case, six in 2 cases, and five in 5 cases. The mathematical average of hypothalamic symptoms resulting from lesions in this group was 4.2. In lesions of the walls of the third ventricle or of its roof, the mathematical average of hypothalamic symptoms

TABLE 2. NATURE OF PATHOLOGIC PROCESS INVOLVING THE HYPOTHALAMUS, IN 60 CASES COLLECTED FROM LITERATURE

Pathologic process involving hypothalamus		No. of cases
A. Neoplasms		
Craniopharyngioma		14
Astrocytoma		8
Hyperplasia (congenital malformation)		5
Infundibuloma		4
Pinealoma		3
Ependymoma		2
Ganglioneuroma		2
Plasmocytoma		1
Neurofibroma		1
Medulloblastoma		1
Perithelial sarcoma		1
Angioma		1
Malignant hemangioendothelioma		1
Cyst of choroid plexus		1
Cyst		1
Undentified tumors		5
	Total	*51*
B. Inflammatory lesions		
Encephalo-meningitis		4
Encephalitis		3
	Total	*7*
C. Degenerative lesions		
Tuberous sclerosis		1
Arteriosclerotic degeneration		1
	Total	*2*

was 2.3. Among 13 cases in this group the highest number of vegetative symptoms in the individual instance was only four (2 cases), and 3 cases showed only one such symptom.

This confirms the observation of Bailey and Fulton (28). They pointed out that lesions originating in the roof of the third ventricle, or from portions of it situated above the floor, produce rather clear-cut pyramidal and sensory disturbances, combined with a typical broad-based shuffling gait, whereas hypothalamic symptomatology is scarce.

Hypothalamic-linked symptoms and signs

The nature of hypothalamic-linked symptoms and signs, their frequency of appearance, and the frequency with which they are the first manifestation of hypothalamic involvement, may be seen in Table 3.

TABLE 3. HYPOTHALAMIC-LINKED SYMPTOMS AND SIGNS. INCIDENCE AND FREQUENCY OF OCCURRENCE AS FIRST MANIFESTATION OF HYPOTHALAMIC DISEASE (60 CASES)

Hypothalamic-linked symptoms and signs		No. of cases	Appearing as first manifestation. No. of cases
Sexual abnormalities			
Precocious puberty	24	43	21
Hypogonadism	19		
Diabetes insipidus		21	2
Psychic disturbances		21	7
Somnolence		18	6
Obesity		15	1
Thermodysregulation		13	4
Emaciation		11	2
Convulsions (automatic crises)		9	1
Disturbances of sphincteric control (urinary, rectal)		5	0
Bulimia		5	2
Anorexia		4	0
Dyshidrosis		4	0

Due to the anatomic neighbors of the hypothalamus—the optic nerve, chiasma, optic tracts, other optic nerves, the internal capsule, cerebral peduncles, and cerebro-cerebellar peduncles—a triad of vegetative-endocrine, ophthalmologic and pyramidal-cerebellar signs can usually be observed, in the sequence enumerated (Table 4).

TABLE 4. NEUROLOGIC SYMPTOMS AND SIGNS. INCIDENCE AND FREQUENCY OF OCCURRENCE AS FIRST MANIFESTATION OF HYPOTHALAMIC DISEASE (60 CASES)

Neurologic symptoms and signs	No. of cases	Appearance as first manifestation. No. of cases
Pyramidal, sensory nerve disturbances	45	1
Neuro-ophthalmologic signs	47	8
Headaches	39	8
Extrapyramidal cerebellar signs	37	4
Vomiting	24	4

Vegetative-endocrine symptoms were the forerunners of hypothalamic disease in 46 cases, and there were 34 cases among these 46 in which the second symptom was also vegetative.

In most instances (38 cases) the hypothalamic involvement became evident clinically during the first fifteen years of life. The time interval elapsing between the first and second symptoms or group of symptoms ranged from less than one year in 8 cases, to twenty-eight years in 2 cases. In 21 cases the interval ranged from three to twelve years; it was more than one year in 7 cases and more than two years in 11 cases.

In general the diagnosis of a brain lesion was not entertained at the time of onset of the first symptom. A systematic neurologic work-up and other studies were usually started in the hospital years later, when a second symptom or several other symptoms appeared. However, it is at the time of onset of the first symptom that it may be relatively easier to make a correct diagnosis. At this juncture, internal hydrocephalus usually has not complicated the picture. According to Bailey and Fulton (28) most of the enumerated hypothalamic symptoms, correctly interpreted and in the absence of internal hydrocephalus, have true localizing, diagnostic significance. In 14 of the 46 cases in which hypothalamic disturbances appeared first, there was no hydrocephalus or increased fluid pressure even at the time of hospitalization, which usually occurred several years after the appearance of the first symptom.

Sexual abnormalities

The most frequent sign of hypothalamic involvement seemed to be modification of sexual function and development. This occurred in 43 of the 60 cases, appearing as the first symptom in 21. Of 35 cases in which the pituitary was examined grossly, there were 33 in which the findings were normal. This was confirmed by histologic examination in 20 cases. In other words, marked alteration of sexual function may be caused by hypothalamic pathology per se in the absence of pituitary pathology.

Precocious puberty

Precocious puberty occurred in 24 cases, 19 males and 5 females. In 4 cases it occurred very early, during the first two years of life; in another 5 cases within the first three to six years of life. The nature of the hypothalamic lesions may be seen in Table 5.

All of the precocious puberty cases had a normal pituitary gland. Microscopic confirmation of an intact pituitary was available in 10 cases. There were no abnormal findings, except an increase of eosinophilic cells in 4 of the cases.

TABLE 5. NATURE OF HYPOTHALAMIC PATHOLOGY IN 24 CASES OF PRECOCIOUS PUBERTY

Pathologic condition involving hypothalamus		No. of cases	
A. Neoplasms			
Astrocytoma		8	
Hyperplasia (congenital malformation)		5	
Ganglioneuroma		2	
Neurofibroma		1	
Ependymoma		1	
Infundibuloma		1	
Pinealoma metastasis to third ventricle		1	
	Total	*19*	*19*
B. Inflammatory lesions			
Tuberculous meningo-encephalitis		1	
Meningo-encephalitis		3	
	Total	*4*	*4*
C. Degenerative lesion			
Tuberous sclerosis	*Total*	*1*	*1*
			24

The observation of Weinberger and Grant (37) and others that an intact pituitary is necessary for postulating the cerebral pathogenesis of precocious puberty, seems to be strongly supported by these findings. Weinberger theorized that premature release of the influence of an inhibitory center in the caudalmammillary region of the hypothalamus set the gonad-stimulating center in the tuber cinereum into early action, effecting release of gonadotropic principle from the pituitary and thus causing premature development and function of the gonads. He pointed out that most of his 17 cases, collected from the literature, showed caudal lesions.

In this collection of 24 cases of precocious puberty, with 10 cases of Weinberger and Grant's included, there were 17 in which a localized lesion could be pointed out. Among these, 14 showed lesions in the posterior hypothalamus, with 9 of them affecting the mammillary bodies. However, 9 other cases, not included in the series of Weinberger and Grant cannot be interpreted this way; they showed diffuse inflammatory, periventricular and encephalitic lesions. There were 5 other peculiar cases, which did not show any distinct damage to the hypothalamus. The pathologic lesions

consisted of minute congenital malformations appended to either the tuber cinereum or the corpora mammillaria; they contained normal or somewhat hyperplastic nerve tissue, usually identical with the specific cells encountered in the tuber cinereum. The authors reporting these cases (13–16) suggested that direct nervous or neurohumoral stimulation from these appendages was transmitted either by way of the tuberogonadal centers to the anterior pituitary, or directly from the tuberogonadal centers down to the gonads.

In precocious puberty the same average number of associated hypothalamic symptoms occurred, as in all the 60 cases, *i.e.*, three symptoms per case. Two patients did not manifest any symptoms except the precocious puberty; such cases present real diagnostic problems. However, if any hypothalamic symptoms appear along with the precocious puberty, one should always strongly consider cerebral origin of the syndrome.

One case with five associated hypothalamic symptoms was diagnosed as adrenal cortex tumor: a laparotomy was performed and the patient succumbed within a day.

Internal hydrocephalus was associated with precocious puberty in 11 instances. There were only 3 cases among the 19 with gonadal depression, which did not show internal hydrocephalus. In the latter group, although internal hydrocephalus may have actually contributed to the depression of sexual function and development, because of pressure on centers in the walls of the third ventricle, it would seem that this pressure in the 11 cases of precocious puberty was either insufficient or too late to prevent the premature sexual development.

Hypogonadism

The 19 cases of hypogonadism occurred in 12 males, and 7 females. The disease became manifest in 8 cases during the first 15 years of life, in 6 cases during the ages between 16 and 30, in 1 case at the age of 31, and in 1 case at the age of 37. In only 3 patients was there destruction of the whole hypothalamus; in 13 the destruction involved one third to two thirds; and in 1 case only a small portion of the median eminence, slightly anterior to the midline, was destroyed.

In 8 instances of hypogonadism a craniopharyngioma was found (Table 6). The growth of this type of tumor, derived from epithelial rests of the hypophyseal duct, takes place from below upwards and caudad. Thus, the hypothalamus is attacked first from the anterior inferior (tuberal) aspect. The craniopharyngiomas from the "upper anlage" are suprasellar tumors. There were 14 craniopharyngiomas, not associated with precocious puberty in any instance. The location of the lesion in cases of gonadal depression, in contrast to that in cases of precocious puberty, was predominantly in

TABLE 6. NATURE OF HYPOTHALAMIC PATHOLOGY IN 19 CASES OF HYPOGONADISM

Pathology involving hypothalamus		No. of cases	
A. Neoplasms			
Craniopharyngioma		8	
Infundibuloma		2	
Pinealoma		2	
Angioma		1	
Cyst of third ventricle		1	
Unidentified tumor		2	
	Total	*16*	*16*
B. Inflammatory lesions			
Meningo-encephalitis		2	
Postinflammatory scar		1	
	Total	*3*	*3*
			19

the inferior (tubero-infundibular) and more anterior region of the hypothalamus. Of the 19 hypogonadal cases, 16 had such lesions in the floor of the third ventricle.

Among 16 cases of the hypogonadal group in which an autopsy was performed, the pituitary was normal in 14, in 10 of which the observation was confirmed microscopically. One of the microscopic analyses of the anterior pituitary revealed a reduced number of basophils; another, proportionately more chromophobe cells than acidophils. In possibly 10, and definitely 8 cases, then, the hypogonadism was not primarily due to anterior pituitary pathology.

In reviewing the experimental literature on this subject, it would seem likely that hypogonadism due to hypothalamic lesions is brought about by an abnormally low release of gonadotropic principles from the anterior pituitary, rather than by influences transmitted by the autonomic nervous system; nevertheless, the latter mechanism has also been proposed by various observers.

Pathologic changes in bone growth

Precocious puberty was practically always accompanied by accelerated bone growth, resulting in overgrowth ranging from 4 to 21 inches (average, 10 inches) above the normal height for the specific age.

Unfortunately, hardly any measurements were available in the other types of patients, except in 2 cases of hypogonadism in which the height was below normal (5 inches below, in 1 case).

Case reports of altered sexual function

In order to illustrate the symptomatology in these patients with alteration of sexual function secondary to a hypothalamic lesion, 2 cases (1 of precocious puberty, and 1 of severe seminiferous tubule failure) are described in more detail.

Example of precocious puberty. The first case of precocious puberty, developing in an infant girl, due to a small hyperplastic lesion attached to the tuberal region of the hypothalamus, is one reported by Seckel *et al.* (13). Enlargement of the breasts occurred at 2½ years. Menstruation began at 3 years, with regular 28-day cycles. At the age of 5 the girl was too tall, showed precocious maturation, but no sexual inclinations. At 7 years of age, glandular tissues were palpable in the enlarged breasts, the uterus was of adult size, and endometrial biopsy showed "endometrial hyperplasia." There were no neurologic signs. The basal metabolic rate was −27 per cent (chronologically normal, −11 per cent). The red blood cell count and hemoglobin were high. There was no psychosexual maturation, and intelligence was normal. Pelvic exploration for ovarian tumor gave negative results; the ovaries showed mature follicles. The child died on the operating table. Autopsy revealed many primordial follicles in the ovaries, and several follicular cysts, but no corpora lutea. All other glands were normal. The brain was large but normal. Beneath the mammillary bodies was an egg-shaped mass, measuring 0.9 by 0.6 cm. approaching the tuberal portion of the hypothalamus. It contained nerve tissue resembling tuber cinereum tissue. There were no neoplastic cells. The pituitary weighed 540 mg. and showed some preponderance of eosinophilic cells. The pathologic diagnosis was: congenital hyperplastic abnormality, hamartoma arising from the tuber cinereum.

Example of hypogonadism. A case of seminiferous tubule failure, associated with degenerative change in the hypothalamus, was reported by Anderson (29). This 30-year-old male had retardation of growth until the age of 12, followed by rapid growth from then on. At the age of 20 he weighed 125 pounds, and his height was 5 feet 11 inches. Pubic hair did not develop until he was 18; he started to shave at the age of 22 (1–2 times weekly). Rapid weight gain then occurred. At the age of 30 the patient weighed 216 pounds. Headaches and blurring of vision followed the onset of obesity, and there were occasional attacks of vomiting, and of "blacking out." A diagnosis of "hypogonadism, intrinsic testicular type" was made. Later on, during hospitalization, attacks of unexplained fever occurred, the temperature rising to 104 degrees F., and returning to normal within two hours. On examination the patient showed very sparse secondary hair growth, a female type of hair distribution in the pubic region, and downy hair on other parts of the body. There was marked girdle obesity. Bending the head forward aggravated headaches and dizziness, and caused moderate hyperhydrosis of palms. The patient was azoospermic. The glucose tolerance curve was somewhat delayed in returning to normal. An air ventriculogram showed dilated lateral ventricles and no filling of the third ventricle. The patient died within two days following craniotomy. The tentative diagnosis was colloid cyst in the third ventricle.

Autopsy.—The adrenals together weighed 25 grams. They were normal microscopically. There was histologic evidence of reduced activity of the thyroid gland. The testes on microscopic examination showed large and small masses of interstitial cells, many of them with abundant, golden brown, granulated pigment. There were some scattered seminiferous tubules, most of them with complete atrophy of the lumen. Only occasional spermatogonia and spermatocytes were seen and there were no inflammatory cells.

The brain showed milkiness and thickness of the arachnoid base region of the third ventricle. Gross and microscopic examination of the hypothalamus at the infundibular level showed a dense cellular scar, midway between the nucleus paraventricularis and the upper surface of the infundibulum. In the region of the median eminence were degenerative changes, especially of the periventricular nucleus, bilaterally. Neural connections with the neurohypophysis were interrupted. The anterior pituitary contained some foamy cells apparently derived from basophils (examination by Rasmussen), but was intact otherwise.

Interpretation of case by author.—The brain lesions were interpreted by Anderson (29) as an end-stage of an old meningoencephalitis. Various literature sources were quoted, showing that lesions in the region of the median eminence repeatedly have resulted in profound reduction in release of both luteinizing and follicle-stimulating hormone.

Diabetes insipidus

Diabetes insipidus was the second most frequent sign of hypothalamic disease, but it was not an early one. In only 2 of the 21 cases of diabetes insipidus was this sign the first evidence of hypothalamic dysfunction. It would surely be rewarding to look more carefully for the opposite manifestation, *i.e.*, water retention, resulting oliguria and excessive concentration of urine.

As far as water metabolism is concerned, it is likely that there are more antagonistic centers than just the known ones in the anterior hypothalamus (supraoptic nuclei and others). Tests to discover such excessive tendencies toward urine concentration have been devised by Zondek (38) and others. From recent reports (39) it would appear that the hypothalamus has some definite share in the control of the level of blood electrolytes. In 18 cases of cerebral lesions (5 with lesions in the hypothalamus), marked hypernatremia and hyperchloremia have been reported. Frequent determinations of blood electrolyte levels should be made in cases suspected of having hypothalamic lesions.

Psychic disturbances

These consisted of such manifestations as violent outbursts of rage accompanied by characteristic motor phenomena, attacks of laughing or crying without reason followed by sleep, and certain patterns of abnormal psychosexual behaviorism.

Psychic disturbances were just as frequent as diabetes insipidus and occurred as first symptoms in 7 cases.

Somnolence

Somnolence occurred in 18 cases, and ushered in hypothalamic disease as the first symptom in 6 cases; thus, it was a very significant sign. A periodically occurring somnolence in a patient who is easily awakened, gains first rank importance in the absence of increased intracranial pressure. Presence of increased pressure by no means rules out hypothalamic involve-

ment; it does, however, suggest the consideration of other seats in the brain, distant from the hypothalamus. Internal hydrocephalus is a rather frequent complication of hypothalamic lesions, because of their early interference with the free flow of cerebrospinal fluid (blocking of the foramen of Monro, or the aqueduct). At least 43 of the 60 cases showed such an interference. One case of reversed sleep and consciousness rhythms was reported, in which the patient was lethargic in the daytime, and very restless and active at night.

Obesity and emaciation

Obesity and emaciation, although each of moderate frequency (15 and 11 cases, respectively) also seemed to be late in appearing as initial symptoms. The pectoral-girdle type of obesity was not as frequently mentioned as one might expect. A generalized obesity, very excessive in some exceptional cases, was the rule.

The amount of food intake, and the degree of polyphagia or anorexia (unfortunately only 9 observers mention abnormal findings) did not always correspond to the findings of obesity or emaciation, respectively. In 3 cases with marked bulimia no obesity resulted; in fact in 1 case the patient was emaciated. Another patient had bulimia, and only much later did obesity develop. One patient had anorexia, but was obese.

Polyphagia in an obese patient, especially when coupled with other autonomic disorders, should by no means dispel our suspicions of a diencephalic lesion, because this organ definitely shares in the regulation of appetite, as Tepperman *et al.* (40) and other observers have demonstrated.

Dysthermia

Another fairly frequent hypothalamic symptom was dysthermia. Davison (25) has worked on this subject from a clinical viewpoint. Some of his reported cases are included here.

Hyperthermia, hypothermia, poikilothermia, and dissociation of correlation of temperature, pulse and respiration, were noted. Unexplained fever was observed in 6 cases, subnormal temperature (below 90° F.) in 7 cases, dissociation of pulse and temperature in 3 cases, and poikilothermia in 1 case.

Even though the heat-dissipation center in the anterior hypothalamus is separate from the caudal heat-maintenance and production center, fibers from the anterior center pass through the caudal part of the hypothalamus. Attempts to show corresponding lesions in the respective centers were, therefore, not too gratifying, as far as localization is concerned.

Here again more systematic observation methods would be necessary to recognize malfunctions. Correlation of pulse, temperature, and respira-

tion curves based on readings taken three times daily in an undisturbed environment, is not enough. Very low temperatures must be registered with a special instrument; and if the mercury column is not reduced to the lowest point before taking the temperature, low degrees will not be recorded. Attempts to observe whether the temperature rose or fell according to the patient's immersion in warm or cold water, were reported only by Davison.

Hypothalamic high temperatures have certain differentiating features. The patient usually does not experience the general malaise, common with high temperatures of toxic origin. The extremities are cold and clammy. The temperature responds to cerebral sedatives, but not to salicylates.

Convulsions

Diencephalic, autonomic crises usually had some or all of these distinguishing features: an aura of compulsive laughing or crying, no loss of consciousness, decerebrate-type rigidity, extreme perspiration, very high pulse rate, low blood pressure, popping eyes, an expression of extreme fright and perfect recollection of all events after the attack.

Miscellaneous symptoms

Acral cyanosis, usually in combination with convulsions, hyperpigmentation, hyper- or hypotrichosis, and disturbance of sphincteric control with urinary and/or fecal incontinence, occurred in a few cases.

Hypothalamic syndromes

Lesions confined to one of the three functional units of the hypothalamus were rare. Specific hypothalamic syndromes with correspondingly confined lesions in the hypothalamus could not be expected therefore to occur with any significant frequency.

Judging from an analysis of the combination patterns recorded, precocious puberty showed very little tendency toward association with obesity, somnolence or diabetes insipidus. This was in contrast to hypogenitalism, in which instance this association was distinctly more frequent. Precocious puberty was outstandingly confined to cases with involvement of the caudal end of the hypothalamus. Cases of hypogenitalism and the mentioned associated symptoms, on the other hand, did not show such strict confinement of the lesion; however, lesions in the anterior infundibulo-tuberal hypothalamus were predominant.

Neurologic Symptons and Signs

Eye signs

Eye signs were present in 47 cases, but in only 8 cases were they the first sign of the disease. They were noted mainly in cases of neoplasm and consisted of such conditions as optic atrophy (often in one eye, with

papilledema in the other eye) visual-field disturbances, external ocular-movement disturbances, and blurring of vision. An excellent evaluation of the diagnostic possibilities from this approach is given in the monograph of Kestenbaum (41) on the subject of neuro-ophthalmology. This author has emphasized important points in differential diagnosis, with regard to infra-, supra- and parasellar lesions which impinge on the optic nervous apparatus.

Most neurologic textbooks flatly declare that eye signs are of no value in localizing lesions of this region. Such statements are made as a result of inadequate neuro-ophthalmologic examination. This was demonstrated in the 60 cases of this series. For instance, in only 1 or 2 of them was there any record of successive visual-field examinations. Observations of the succession in which parts of the visual fields are narrowed, however, furnish important, differential-diagnostic information. Apparently, tangent-screen examinations were made use of to a very limited extent, since central scotomata were hardly mentioned. The latter may often be missed with the usual methods. Only one report mentioned the use of color fields. Less conspicuous visual-field defects may be missed with the ordinary white-field examination.

Signs of pyramidal and sensory nerve involvement

Pyramidal and sensory nerve disturbances occurred in 45 of the 60 cases. Only 1 case showed a strictly neurologic sign of this category as an initial symptom. Contrary to the usual textbook emphasis on headaches and vomiting as foreboding symptoms of brain tumor, headaches appeared as the first symptom in only 8 cases, vomiting in 4 cases, and vertigo in 2 cases.

Disturbance of sphincteric control with urinary and/or fecal incontinence occurred in 5 cases.

LABORATORY OBSERVATIONS

Basal metabolic rate and cholesterol

The basal metabolic rate was reported in only 10 cases. In 9 it was low or borderline-low; however, only 6 of these patients had a normal pituitary. In 4 cases, in which blood cholesterol levels were also given, these were disproportionately low; 3 of these 4 patients had intact pituitaries.

Glucose tolerance curves

In 10 cases glucose tolerance tests were made; in 3 of these the results were normal. One 67-year-old female seemed to have diabetes mellitus; whether it resulted from her degenerative arteriosclerotic lesion in the hypothalamus is questionable. There was delay of return of the blood

glucose level to normal in 3 cases; 3 other cases showed rather flat curves. Only the patient with diabetes mellitus showed sugar in the urine; another patient repeatedly showed urinary acetone and diacetic acid. In none of the other 58 cases was any sugar found in the urine. Glucose tolerance tests are very important, if one is to demonstrate disturbances in glucose metabolism in these cases. Among the patients with flat curves were those with precocious puberty associated with small hyperplastic appendages to the hypothalamus. The other patients with abnormal glucose tolerance curves had lesions in the floor of the third ventricle, toward the caudal region.

COMPARISON OF TENTATIVE AND AUTOPSY DIAGNOSIS

The analysis of tentative diagnosis as compared to autopsy diagnosis was rather interesting. Among 52 cases in which a tentative diagnosis was made, the correct diagnosis was missed in 31—which is still a good percentage, considering the difficulties involved. In 6 cases even an air ventriculogram was of no help.

In 6 cases a neoplasm was wrongly diagnosed as an inflammatory lesion. In 5 cases the reverse occurred. The first source of error very often stems from colloid cysts, perforating and emptying their irritating contents into the ventricular system. The second error may arise because of dilatation of the third ventricle, imitating a space-occupying, expanding lesion.

In 5 instances laparotomy was performed in an attempt to locate an endocrine lesion in the adrenal cortex or the ovaries in the cases of precocious puberty. At least in 1 case this operation was more or less exploratory, with the possibility of a diencephalic lesion in mind. Naturally a laparotomy involves less trauma than craniotomy, especially in the case of suspected lesions in the caudal hypothalamus; the prognosis in the latter case is rather hopeless in any event. Patients with hypothalamic lesions are rather ill-equipped to cope with operational stress. One of the patients died on the operating table, and 2 other patients died within two days after the laparotomy.

In 4 cases the tentative diagnosis of tumor of the posterior fossa was made, and in 3 of these a suboccipital craniotomy was performed, with negative findings. Neoplasms in the hypothalamic region, by way of least resistance, tend to expand through the interpeduncular space and exert pressure on the cerebrocerebellar connective arms, thus misleading the examiner.

The crux of the matter is, that tumors of the posterior fossa, tending to induce internal hydrocephalus, may be accompanied by hypothalamic symptoms due to increased pressure in the third ventricle. In a patient with hypothalamic symptoms and cerebellar symptomalogy, the hypo-

thalamus as the seat of the lesion should be given first choice, in the absence of internal hydrocephalus.

CONCLUSIONS

Sixty cases of neoplastic, inflammatory and degenerative disease in the hypothalamus have been analyzed as to their prevalent signs and symptoms and autopsy findings. The majority exhibited a multiplicity of altered hypothalamic functions, and in these instances at least two thirds of the hypothalamus was destroyed. The extent of destruction of this organ, however, did not necessarily correspond to the degree of alteration in vegetative functions. The average number of such symptoms or signs in the individual case was three.

Vegetative symptoms appeared before neurologic or neuro-ophthalmologic signs became manifest. The localizing value of these signs has been stressed, as has also the time lag, which in many of these cases extends over several years, from the first discovery of an autonomic nervous system disorder to the time of systematic neurologic work-up.

The incidence of the hypothalamic symptoms and the frequency of their appearance as an initial symptom has been described.

The most frequent expression of hypothalamic pathology was alteration of sexual development, maintenance and function. Two cases, one of precocious puberty and the other of seminiferous-tubule failure have been described in detail. The localization of the hypothalamic lesion in the caudal part of the diencephalon in most cases of precocious puberty, and in the tubero-infundibular region in most cases of hypogonadism, was confirmed.

An analysis of clinical diagnoses and autopsy reports revealed the difficulties involved in differential diagnosis. Three suboccipital craniotomies and 5 laparotomies were performed in search for pathologic lesions in those areas, rather than in the hypothalamus. Three patients of the laparotomy group died within two days after operation. The advisability of this operation in cases of precocious puberty accompanied by other hypothalamic signs, is questioned, even if performed as a means of exploration of the adrenal cortex or ovaries. The impaired adaptation mechanism of these patients to operational stress should be taken into account.

The surgical results, as well as the time lag noted before specific diagnostic measures were taken to investigate the possibility of hypothalamic pathology, not only emphasize the diagnostic difficulties, but also indicate an unfamiliarity with, or unwillingness to attach due importance to hypothalamic symptomatology. Excellent, authentic material is available in this field, so far as animal research is concerned, but more carefully evaluated clinical material is much to be desired.

REFERENCES

1. Schmalz, A.: Ueber einen Fall von Hirntumor mit Pubertas praecox, *Beitr. z. Path. Anat. u. z. allg. Path.* **73:** 168, 1925.
2. Gross, Robert E.: Neoplasms, producing endocrine disturbances in childhood, *Am. J. Dis. Child.* **59:** 579, 1940.
3. Papez, James W., and Ecker, A.: Precocious puberty with hypothalamic tumor (infundibuloma), *J. Neuropath. & Exper. Neurol.* **6:** 15, 1947.
4. Bailey, P.; Buchanan, D. N., and Bucy, P. C.: Intracranial Tumors of Infancy and Childhood. Chicago, Univ. of Chicago Press, 1939, Case 68.
5. Vickers, W., and Tidswell, M. J.: Tumor of hypothalamus, *M. J. Australia* **2:** 116, 1932.
6. Saar, Heinrich: Pubertas praecox bei Gliom des Zwischenhirns. Ein Beitrag zur Frage der innersekretorischen Funktion der Zirbeldruese, *Frankfurt. Ztschr. f. Path.* **50:** 451, 1937.
7. Horrax, G., and Bailey, P.: Pineal pathology; further studies, *Arch. Neurol. & Psychiat.* **19:** 394, 1928.
8. Heuyer, G.; Lhermitte, J., and Vogt, C.: Un cas de macrogénitosomie précoce liée à un épendymogliome de la région mamillo-tubérale, *Rev. neurol.* **2:** 194, 1931.
9. Clark, W. E. L.; Beattie, J.; Riddoch, G., and Dott, N. M.: The hypothalamus. Morphological, functional, clinical and surgical aspects. The Henderson Trust Lectures, Nos. 13–16, published for the William Ramsey Henderson Trust. Edinburgh and London, Oliver & Boyd, 1938.
10. Poston, H., and Barber, A. H.: External genital hypertrophy in infancy, *Lancet* **1:** 384, 1942.
11. De Lange, C.: Zur Klinik und pathologischen Anatomie der hypothalamischen Form von Pubertas praecox, *Ann. paediat.* **161:** 113, 1943.
12. Clement, Robert: Macrogénitosomie précoce et gliome astrocytome de la région opto-chiasmatique, *Bull. et mém Soc. méd. d. hôp. de Paris* **58:** 333, 1942.
13. Seckel, H. P. G.; Scott, W. W., and Benditt, E. P.: Six examples of precocious sexual development; studies in diagnosis and pathogenesis, *Am. J. Dis. Child.* **78:** 484, 1949.
14. Spatz, B.: Hypothalamic form of precocious puberty, *Deutsche med. Wchnschr.* **2:** 1956, 1929.
15. Le Marquand, H. S.: Case of pubertas praecox (macrogenitosomia praecox) in boy, associated with tumour in floor of third ventricle, *Roy. Berkshire Hosp. Rep.* pp. 31–61, 1934–1935.
16. Bronstein, I. P.: Sexual precociousness, associated with hyperplastic abnormality of tuber cinereum, *Am. J. Dis. Child.* **64:** 211, 1952.
17. Tannhauser, S. J.: Neurofibromatosis (Von Recklinghausen) and osteitis fibrosa cystica, localisata et disseminata. Common pathogenesis, *Medicine* **23:** 105, 1944.
18. Horrax, Gilbert, and Bailey, P.: Tumors of the pineal body, *Arch. Neurol. & Psychiat.* **13:** 423, 1925.
19. Hellner, Hans.: Ueber Pubertas praecox, im besonderen die hypothalamische Form, *Med. Klin.* **32:** 1619, 1936.
20. Thomas, A., and Schaeffer, H.: Un cas de macrogénitosomie précoce avec hydrocéphalie, lésions inflammatoires de la région infundibulotubérienne et symphyse cervicale, triméningée, sans néoplasme intercranien, *Rev. neurol.* **2:** 595, 1931.
21. Poos, F.: Ueber eine seltene chronische Verlaufsform tuberkuloeser Meningo-encephalitis, *Klin. Monatsbl. f. Augenh.* **95:** 537, 1935.

22. KRABBÉ, K. H.: La sclérose tubéreuse du cerveaux et l'hydrocéphalie dans leur relations avec la puberté precóce, *Encéphale* **17:** 281, 1922.
23. COLLINS, VINCENT P.: Effects of destruction of hypothalamus by tumor, *Arch. Neurol. & Psychiat.* **46:** 774, 1942.
24. GLOBUS, JOSEPH H., and GANG, K. M.: Craniopharyngioma and suprasellar adamantinoma, *J. Mt. Sinai Hosp.* **12:** 220, 1945.
25. DAVISON, CHARLES: Disturbances of temperature regulation in man; clinico-pathologic study, *Proc. A. Res. Nerv. & Ment. Dis.* (1939) **20:** 774, 1940.
26. GLOBUS, JOSEPH H.: Infundibuloma; newly recognized tumor of neurohypophysis, *J. Neuropath. & Exper. Neurol.* **1:** 59, 1942.
27. CLEGHORN, H. H.: Hypogonadism, associated with invasion of the midbrain and hypothalamus, *Quart. J. Med.* **7:** 183, 1938.
28. BAILEY, PERCIVAL, and FULTON, J.: Tumors in the region of the third ventricle; their diagnosis and relation to pathologic sleep, *J. Nerv. & Ment. Dis.* **69:** 1, 1929.
29. ANDERSON, EVELYN: Seminiferous tubule failure, associated with degenerative change in the hypothalamus, *Am. Pract. & Digest. Treat.* **1:** 41, 1950.
30. AYALA, G.: Syndrome végétatif: méningo-encéphalite hypothalamique strictement limitée (hypothalamo-méningite), *Rev. neurol.* **1:** 975, 1934.
31. MOORE, R. A., and CUSHING, E. H.: Diabetes insipidus and Fröhlich's syndrome, associated with encephalitis of hypothalamic region, *Arch. Neurol. & Psychiat.* **34:** 828, 1935.
32. FINE, BERNHARD D.: Infundibuloma; case report with review of literature, *J. Mt. Sinai Hosp.* **14:** 28, 1947.
33. FRENCH, DOUGLAS J.: Plasmo-cytoma. Clinical-pathologic report of case, *J. Neuropath. & Exper. Neurol.* **6:** 265, 1947.
34. THOMAS, A., and others: Examen histologique d'une tumeur de la région infundibulo-tubérienne. Neurospongiome. Absence de symptômes d'ordre végétatif, *Rev. neurol.* **1:** 952, 1934.
35. DRAGANESCO, S., and SAGER, O.: Contributions à l'étude du système végétatif diencéphalique (observation anatomo-clinique d'un cas d'épendymocytome kystique du III^{e} ventricule), *Rev. neurol.* **1:** 959, 1934.
36. SUNDERMAN, WILLIAM F.: Hypothermia and elevated serum magnesium in patient with facial hemangioma, extending into hypothalamus, *Am. J. M. Sc.* **213:** 562, 1947.
37. WEINBERGER, LAURENCE, M., and GRANT, F. C.: Precocious puberty and tumor of hypothalamus, report of case and review of literature with patho-physiologic explanation of precocious sexual syndrome, *Arch. Int. Med.* **67:** 762, 1941.
38. ZONDEK, HERMANN: The Diseases of the Endocrine Glands, ed. 4. Baltimore, The Williams & Wilkins Co., 1944, p. 262.
39. COOPER, IRVING, S., and CREVIER, PAUL H.: Neurogenic hypernatremia and hyperchloremia, *J. Clin. Endocrinol. & Metab.* **12:** 821, 1952.
40. TEPPERMAN, J.; BROBECK, J. R., and LONG, C. N. H.: Effects of hypothalamic hyperphagia and of alteration in feeding habits on metabolism of albino rat, *Yale J. Biol. & Med.* **15:** 855, 1943.
41. KESTENBAUM, ALFRED: Clinical Methods of Neuro-Ophthalmologic Examination. New York, Grune & Stratton, 1947.

ACROMEGALY AND PREGNANCY

WILLIAM A. ABELOVE, M.D.,* J. J. RUPP, M.D. AND KARL E. PASCHKIS, M.D.

The Division of Endocrine and Cancer Research, Jefferson Medical College, Philadelphia, Pennsylvania

THE occurrence of two normal pregnancies in an acromegalic female afforded an opportunity for a detailed study of this rather unusual relationship. A review of the world literature revealed 33 reported cases of pregnancy occurring in patients with acromegaly. Because of this uncommon association, a case is being presented, together with a summary of the world literature and discussion concerning the physiology of the pituitary-gonadal system in acromegaly and in pregnancy.

The anterior pituitary in pregnancy

Following early descriptions of the anterior pituitary in pregnancy (Comte (1), Erdheim and Stumme (2), Schauta (3)), it is now well recognized that the adenohypophysis enlarges to about twice its normal size during gestation. The early investigators described an acidophil-like cell of chromophobe origin, referring to it as the "pregnancy cell" (2) and relating the gross enlargement in size and weight of the hypophysis to the development of these cells in the anterior lobe (3).

Severinghaus stated that the "pregnancy cell" is an acidophilic cell in a state of high secretory activity, developing from the chromophobes and reverting to that state after the termination of pregnancy. Cytologic examination of anterior lobes from pregnant animals indicated that both acidophils and basophils are in an active phase of secretion. The pregnancy changes in the anterior lobe indicate excess activity, both of production and release of hormone, with a depletion of stored product. The acidophils are especially involved in the later stages of pregnancy. The important fact to keep in mind, according to Severinghaus, is that the pregnancy cell is probably not a distinct cell type, but rather some transitional aspect of the chromophobe-to-chromophil-to-chromophobe changes which occur in the normal secretory cycle of the cells, but which are greatly accentuated in the active pituitary gland during pregnancy (4). The pituitary reverts

Received for publication May 21, 1953.

* Fellow of the National Institute of Arthritis and Metabolic Diseases, United States Public Health Service.

to normal within a few months postpartum. Evans and Simpson in 1929 found that although the pituitary is increased in size during pregnancy and there is an increase in the urinary excretion of gonadotropins, the actual gonadotropic content of the pituitary, as determined by pituitary implants in immature animals, is extremely small (5). It was shown later that actually the pituitary has little or no gonadotropic activity during pregnancy (6a). The posterior or infundibular lobe of the hypophysis does not hypertrophy during gestation.

The enlargement of the pituitary varies in different cases and at times the gland may even project out of the sella turcica (7). There are numerous conflicting reports regarding the visual-field changes in pregnancy. Lohlein found bitemporal hemianopia in 78 per cent of all pregnant women towards the end of gestation (8). Comans and Beauvieux likewise found that one third of pregnant women have bitemporal contraction of their visual fields with a smaller percentage having superior quadrant cuts (9). McCurry, on the other hand, failed to confirm the findings of the visual-field defects (10). Johns found definite concentric contraction of form and color fields and enlargement of the blind spot in the majority of cases. These changes, she concluded, not being of the type classically seen in association with pituitary disease, probably depend upon functional modifications outside the hypophysis, rather than upon enlargement or vascular changes in the pituitary gland itself (11). Shimkin after a detailed study of the literature and on the basis of his own examinations, concluded that bitemporal hemianopia in pregnancy, attributed to a compression of the chiasma by an enlarged pituitary, occurs only if the pituitary changes of pregnancy are associated with a tumor of the hypophysis, either present before, or developing during pregnancy (12).

Transient "acromegaly of pregnancy"

The increase in size of many pregnant women is very suggestive of greater production of growth hormone during gestation. Because of the known relationship existing between abnormalities of the hypophysis and the development of acromegaly, a similar relationship has been suggested to explain the nonedematous thickening of the features as well as of the extremities, which is observed in many pregnant women (13). This phenomenon has been described by Fruhinsholz in a case report concerning a "dainty woman" who, after a normal pregnancy followed by a miscarriage at two months, became pregnant a third time. The development of thickening of the face and nose and enlargement of the hands and feet presented a picture similar to that in acromegaly. There was no glycosuria or visual disturbance, but severe headaches were present. Following an uncomplicated delivery, the clinical signs disappeared and the patient

returned to normal within a few months post partum. Fruhinsholz refers to this as "acromegalie gravidique" (acromegaly of pregnancy) (14). Transitory acromegaly occurring during pregnancy has also been reported by Marek (15). He cited an instance of acromegalic symptoms occurring during pregnancy in a 23-year-old primipara. The nose, tongue and jaws became larger; the teeth were spread apart; the hands increased in circumference; the tonsils swelled, and glycosuria and muscle pains appeared. All these signs disappeared during the puerperium.

Acromegaly developing during and after pregnancy

In contradistinction to this acromegaly-like syndrome in pregnant women, permanent acromegaly develops in some women during or after gestation.

Cushing presented a case in which there was suggestive evidence of glandular overactivity accompanying early pregnancies, with subsequent development of acromegaly following the fourth pregnancy. He discussed the possible effect which repeated childbearing may have in exciting the gland to a state of pathologic overactivity and concluded that any indications of hypophyseal irritability which accompany childbearing should serve as a definite warning against its immediate repetition (16). Frankl cited an instance of a 27-year-old woman with one previous normal pregnancy. The second pregnancy was uneventful until the seventh month, when sudden impairment of vision occurred, rapidly progressing to total blindness with severe headaches. No other symptoms were present and delivery was normal. A few weeks post partum there was complete return of vision, with concomitant development of acromegalic features (17). Hurxthal *et al.* reported a case in which the onset of acromegaly occurred after pregnancy in a 32-year-old female, amenorrhea and persistent lactation being associated symptoms (18). In Davidoff's review of 100 cases of acromegaly, including 56 females, the onset of the disease dated from the time of pregnancy in 6, the catamenia never having become reestablished post partum (19a). These instances are rare. In most cases of acromegaly in females there is no relation to antecedent pregnancy.

Menstrual and genital changes in acromegaly

Before citing the cases of acromegalic women who became pregnant some time after acromegaly was established, a brief review of menstrual and genital changes in acromegaly is given. Irregularity in the menstrual pattern is one of the earliest and most common findings in acromegaly. In most female patients, according to Davidoff, oligomenorrhea or amenorrhea occur early in the disease (19b). Eighty-seven per cent have dis-

turbances of the menstrual cycle and 73 per cent have complete amenorrhea (20).

Engelbach stated that during the early stage of hyperactivity, there is hypersexuality, due to secondary gonadal stimulation; this is associated with increased fertility, as manifested by supraovulation in the female. The later stages of inactivity are accompanied by a diminution in libido, and by sterility (21). The amenorrhea of acromegaly is almost always associated with sterility. Pregnancy in an acromegalic woman practically never occurs after the development of amenorrhea, although acromegalic women can bear children if their menses continue (19b). Henderson (22) studied 367 cases of pituitary tumor at the Peter Bent Brigham Hospital in an attempt to determine the correlation between the degree of expansion of the sella turcica and disturbances in sexual function. He reported on 73 females with acromegaly. Of these, 7 had had an early hysterectomy; 23 were unmarried; 12 were married but approaching the menopause, the last child having been born many years before the onset of the disease; and 12 became amenorrheic soon after the onset of the disease. There remained 19 young married women who continued to menstruate after acromegaly was apparent. In 6 of them (32 per cent) a normal pregnancy occurred with full-term delivery; 3 of them became pregnant twice. Henderson also mentioned that exacerbations of acromegalic symptoms are known to occur during successive pregnancies. He concluded that sexual dysfunction occurs only when the sella has become considerably expanded, and that this is due solely to compression of the basophilic cells by the space-taking lesion. The observation that the normal menstrual cycle may be resumed and pregnancy may occur after successful radical extirpation of the adenoma, is in agreement with the interpretation that the sexual dysfunction is due to pressure. The fact that there is no difference in this respect between eosinophilic and chromophobe adenomas offers further support. Hurxthal *et al.* confirmed these findings, stating that one of the best indications of successful treatment by radiation is the subsequent re-establishment of menstruation (18). Cagnetto reported a patient in whom menstruation ceased at the age of 19 years, reappearing at the age of 46 and continuing to the age of 48, at which time it disappeared permanently. Autopsy showed cystic degeneration of the tumor of the pituitary. This suggests that even after long continued amenorrhea, the follicular apparatus may not degenerate entirely (23).

Albright divided acromegalics into three groups, namely, those with normal, low, or high urinary FSH excretion, respectively. In the presence of normal levels, pregnancy can occur and be carried to term (24).

Various authors have described changes occurring in the female genital

tract in acromegaly. Montes in a review of the literature involving the sexual changes of acromegalic women, concluded that almost any change can occur and that none occurs regularly (25). Falta stated that in the acromegaly of adults there is usually sharp accentuation of the secondary sexual characteristics, with hyperplasia of the external genitalia, appreciable increase in the dimensions of the labia majora and clitoris, and increase in hair growth, often of a masculine type. These phenomena, may persist until the end of the disease (26). Zondek found that impairment of sexual function in most patients is not associated with retrogressive changes in the secondary sexual characteristics. In both sexes the external genital organs may retain their natural size or even become larger (27). Teel described a case of advanced acromegaly of seven years' duration in a single, 49-year-old woman. There had been no interruption of the catamenia; in fact, menorrhagia was present and a hysterectomy was performed for a suspected fibroid. There was marked diffuse hypertrophy of the uterus and of the entire genital tract, but no uterine mass was found. This picture was an example of the visceral splanchnomegaly that characterizes the disease (28). Pirie, in his case of a 43-year-old married woman with acromegaly of twelve years' duration, found a capacious vagina, a uterus diminished in size as measured by the uterine sound, and an hypertrophied clitoris (29). Putnam and Davidoff noted that the condition of the ovaries has received little attention. In most autopsies the ovaries have been characterized as "atrophic." The one feature in which histologic descriptions agree is the absence of follicles (20). Tandler and Gross found total regression of the primordial follicles and cessation of formation of the Graafian follicles (30). Atrophy of the internal genitalia was found in 36.4 per cent of 118 cases, according to the statistics of Creutzfeldt (31). Goldberg and Lisser reported the premortem and postmortem findings in a 43-year-old acromegalic Negress. At the age of 33 the breasts were moderately developed and the external genitalia normal. Menstrual irregularity appeared at the age of 24, followed one year later by complete amenorrhea. Death occurred at the age of 43, by suicide; at autopsy completely sclerotic ovaries with atrophic breasts and uterus were found (32). Cushing and Davidoff described a case in which the uterus appeared normal in size and the ovaries small and fibrous. They quoted a case of Löwenstein, involving a young woman who died at the age of 16, after five years of evident acromegaly. The ovaries were described as showing an absence of follicles, the entire organs consisting of connective tissue stroma in which were vessels lined by a single layer of cuboidal epithelial cells. They also quoted 2 cases of Kraus. In one, a woman of 34, the ovaries were free from follicles but rich in corpora atretica. In the other, a woman of 54, one of the ovaries, though free from follicles, abounded in stroma through

which there were scattered many cystic spaces lined by cylindrical epithelium; the other ovary was composed of multilocular cysts with a pseudomucinoid element (33).

Apparently, as long as gonadotropic stimulation is forthcoming, the genital tract is capable of overgrowth along with other parts of the body. When the gonadotropins fail, however, as is usually the case rather early in the disease, the internal genital organs gradually atrophy.

REVIEW OF CASES

A careful survey of the world literature regarding pregnancy associated with acromegaly has revealed 35 reported cases. In 2 of these, the diagnosis of acromegaly is questionable, leaving 33 confirmed cases. Soler in 1950 presented 2 cases, with a review of 16 others (34). He cited 2 patients with amenorrhea associated with acromegaly, both of whom had restoration of normal menstrual function, one after radiation therapy, the other following operation; each subsequently became pregnant. In his review, Soler referred to 16 other cases. We have been able to find the original publications in 10 of these (16, 25, 26, 29, 35–39); in one of the 10, the diagnosis appears doubtful (36), and in the other, the relation of the acromegaly to pregnancy is not clear (25). The original reports in the 6 other cases could not be located (40–45). Soler concluded that the coincidence of acromegaly and pregnancy is rare.

Henderson, in a review of 367 cases of pituitary tumor at the Peter Bent Brigham Hospital (quoted previously) reported on 73 females with acromegaly. Of 19 young married women who continued to menstruate after acromegaly was apparent, 6 had a normal pregnancy with full-term delivery, 3 having become pregnant twice (22).

Albright, Reifenstein *et al.* mentioned 2 cases of pregnancy in acromegalics (46). Atkinson (47) stated that pregnancy is not uncommon after acromegaly has developed, and quoted cases reported by Falta (26), Pirie (29), Kalledey (36), and Garnier and Santenoise (48). The latter two reports, however, concerned patients in whom the diagnosis of acromegaly may be questioned. Morgan reported the case of a 34-year-old primipara with acromegaly manifested by clinical signs and by enlargement of the pituitary fossa; she was first seen when three months pregnant. At the time of his report, the gestation has progressed to thirty-six weeks with no aggravation of symptoms (38). Jackson presented a female acromegalic who, following partial removal of an acidophilic adenoma, showed marked improvement in her visual acuity and fields. She was married six weeks after the operation; although amenorrheic, a year later she became pregnant and delivered normally. Complete amenorrhea followed for eight

years; then in the course of the next year she had six periods, again became pregnant, and had an uneventful delivery (49). Bringle cited an instance of a female acromegalic who, following operation and pituitary irradiation, had return of menstrual function, conceived, and carried to term (50). Falta's observation XXIX concerned a patient whose acromegaly developed gradually between the twentieth and thirtieth years of life. She first menstruated at the age of 22; her periods were always rather profuse, lasting two to three days and occurring regularly at four-week intervals. She had 5 normal term pregnancies, the first occurring when she was 28, the last when she was 40. The menopause occurred in her forty-sixth year (26).

Cushing reported a case in which the patient had 4 normal pregnancies; acromegaly became manifest after the birth of the fourth child. In the next six years, she had 3 miscarriages and then succeeded in carrying a pregnancy to term. In his discussion, Cushing mentioned the possible effect which repeated childbearing may have in exciting the pituitary gland to a state of pathologic overactivity (16). In Pirie's case, there was a history of conception occurring three months after the onset of amenorrhea and other symptoms of acromegaly (29). Hurxthal and Dee presented an instance in which pregnancy occurred in a patient with normal gonadotropic function in whom acromegaly had obviously been present for some years (51). A case of pregnancy in a woman 40 years of age, who had had acromegaly for nine years, was reported by Kloppner. Periods were very scant, every six months, for about two years prior to pregnancy. Following a normal term delivery, there was recurrence of menses within four weeks and regularity for the next two years, at the end of which time the report was published (35). The history of a 35-year-old acromegalic female with failing vision was reviewed by Starr and Davis. Two months after resection of the tumor she menstruated, and was delivered of a normal baby eighteen months later (52). Weinstein reported a case in which the patient received deep roentgen-ray therapy to the pituitary, with relief of most of her symptoms. Eight years later a normal term pregnancy occurred (53). Single cases have also been reported by Sturma (twin pregnancy) (54), Schur (55), and Loewenberg (56).

CASE REPORT

M. R., a 29-year-old white clerical worker, was first seen in the Endocrine Clinic of the Jefferson Medical College Hospital on October 1, 1952, referred from the Obstetrical Clinic for evaluation of acromegaly associated with pregnancy. She had no complaints referable to her physical appearance and sought medical attention because of gestation of twenty-three weeks' duration. The patient was admitted to the Jefferson Medical College Hospital on October 6, 1952, for study.

Past medical history revealed an increase in the size of her hands and feet with en-

largement and coarseness of her facial features, of ten to twelve years' duration. There were no headaches or visual disturbances, except "eye strain" at the age of 17, for which she had refraction tests and was given glasses. Over the twelve-year period there had been a gradual increase in her shoe size (from 6½ at age 19, to 10 at age 29) and glove size. There was no polydipsia, polyphagia, polyuria, hirsutism or hyperhidrosis.

Menarche occurred at the age of 12; periods were regular at 28-day intervals, lasting from four to seven days; she had had one pregnancy and delivered at term, spontaneously, in May of 1950; the male child weighed 8 pounds. Her last menstrual period began April 12, 1952.

As a child she had measles, chicken pox, mumps, scarlet fever and head and scalp injuries on three different occasions, none with any loss of consciousness. Her mother was living and well, aged 52; her father died at the age of 59 (suicide). There were no siblings. Family history disclosed a paternal aunt (deceased for thirty years) whom this patient closely resembled.

Physical examination revealed a typically acromegalic 29-year-old white female weighing 150 pounds, and 5 feet 7 inches tall. The following findings were of significance: broad face; large and coarse lips, nose, ears and tongue, with hypertrophy of the lingual papillae; marked separation of the teeth; an increase in the A-P diameter of the chest; mild scoliosis with the primary thoracic curve to the left; large and spade-like appearance of the feet and hands, with inability to flex the hands tightly. The skin and mucous membranes were normal. There was no marked prominence of the supraorbital ridges; no goiter was palpated, and no hepatosplenomegaly was present. The voice was of normal quality and the heart and lungs did not show any abnormal findings. Blood pressure was 130 systolic and 80 diastolic; the pulse was regular, with a rate of 88; the temperature was 98.6° F.; and respirations were 20 per minute. Examination of the abdomen revealed the uterus to be enlarged to the level of the umbilicus, with fetal movements palpated and fetal heart sounds audible. The pelvimetry measurements were: interspinous 24.5 cm., intercristal 29.0 cm., intertrochanteric 30.0 cm., and external conjugate 23.0 cm.

The following *laboratory studies* were made during the period of hospitalization: blood —hemoglobin 12.6 Gm. (81 per cent), erythrocytes 4.4 million per cu. mm., and leukocytes 6,500 per cu. mm. with 72 per cent neutrophils, 26 per cent lymphocytes, and 2 per cent eosinophils; urine (catheterized)—sp.gr. 1.017, reaction alkaline, no albumin or sugar, and no abnormal findings on microscopic examination; serum—concentration of calcium 9.6 mg., inorganic phosphorus 2.85 mg., alkaline phosphatase 2.35 Bodansky units, uric acid 4.8 mg. and protein-bound iodine 5.9 micrograms per 100 ml.; basal metabolic rate +13 per cent with a pulse of 88; blood glucose values following the oral administration of 100 Gm. of glucose—fasting 75 mg., 1 hour 125 mg., 2 hours 85 mg., 3 hours 92 mg., and 4 hours 72 mg. per 100 ml.; blood sedimentation rate (Wintrobe) 34 mm. in one hour; EKG within normal limits; urinary excretion of neutral 17-ketosteroids 9.0 mg. per twenty-four hours; urinary pregnanediol 9.5 mg. per twenty-four hours (method of Sommerville (57a, b)) and 19.2 mg. per twenty-four hours (method of Venning (58a, b)); and urinary formaldehydogenic steroids 1.24 mg. per twenty-four hours. A roentgenogram of the skull failed to reveal any erosion or ballooning of the sella turcica; the sinuses were normal; however, definite tufting of the terminal phalanges of all the extremities was present; in addition, a large enchondroma of the right first rib was noted. Ophthalmoscopic and visual-field examinations showed nothing abnormal.

The diagnosis of pregnancy associated with acromegaly in an inactive phase was made, and the patient discharged to the Endocrine and Maternity Out-Patient Departments.

Subsequent course

The patient was seen at intervals of from two to three weeks and experienced a completely uneventful antenatal course. Periodic laboratory studies were made, and failed to reveal any evidence of activation of the acromegaly.

Thirtieth week of gestation. The basal metabolic rate was +14 per cent, with a pulse of 82; urinary excretion of neutral 17-ketosteroids was 5.1 mg. per twenty-four hours.

Thirty-third week of gestation. Laboratory determinations showed the following concentrations in serum: calcium 9.6 mg., inorganic phosphorus 3.35 mg., uric acid 5.4 mg., and protein-bound iodine 8.2 micrograms per 100 ml. The blood glucose values following the oral administration of 100 Gm. of glucose were: fasting 77 mg., 1 hour 123 mg., 2 hours 116 mg., 3 hours 103 mg., and 4 hours, 92 mg. per 100 ml. Urinary pregnanediol excretion was 62.5 mg. per twenty-four hours (method of Sommerville (57a, b)).

Thirty-sixth week of gestation. Urinary formaldehydogenic steroid excretion was 1.07 mg. per twenty-four hours.

Delivery. On January 19, 1953, the patient was delivered spontaneously, under local anesthesia, of a male child weighing 8 pounds 1½ ounces and measuring 48 cm. in length. Labor lasted three hours and twenty minutes, and delivery was uneventful. The baby was normal on physical examination and was breast fed. There was no appreciable change in the acromegaly of the mother.

Post partum. The following laboratory studies were performed during the immediate 48-hour postpartum period: blood—hemoglobin 12.2 Gm. (78 per cent), erythrocytes 4.32 million per cu. mm., and leukocytes 7,100 per cu. mm.; basal metabolic rate +33 per cent with a pulse of 84; serum—concentration of protein-bound iodine 10.5 micrograms, calcium 8.8 mg., inorganic phosphorus 3.7 mg., alkaline phosphatase 3.58 Bodansky units, uric acid 4.9 mg., and cholesterol 260 mg. per 100 ml.; blood glucose values following the oral administration of 100 Gm. of glucose—fasting 80 mg., 1 hour 145 mg., 2 hours 131 mg., 3 hours 100 mg., 4 hours 80 mg., 5 hours 68 mg., 6 hours 85 mg. per 100 ml.; and urinary excretion of neutral 17-ketosteroids 8.2 mg. per twenty-four hours. Visual fields were normal and roentgenograms of the skull and extremities revealed no change since the previous examination. A urine specimen obtained by catheterization two days post partum contained albumin (++) and sugar (3.3 per cent). Subsequently the urine repeatedly showed no albumin but did show sugar in concentrations varying from ½ to 2 per cent. The fasting blood sugar level on the fifth postpartum day was 112 mg. per 100 ml. The patient was discharged at this time at her own request, to be followed in the out-patient department. One week later her urine was free from sugar.

Within one month normal menstrual periods returned. The baby was breast fed for five weeks and then given formula feeding.

DISCUSSION

The diagnosis of acromegaly was made on the basis of the physical examination and of roentgenologic studies revealing tufting of the terminal phalanges. The absence of roentgenographic changes in the sella turcica does not militate against a diagnosis of acromegaly. According to the work of Henderson (22), one would expect that in the great majority of cases the likelihood of normal gonadotropic function is much less if the eosinophilic adenoma is large enough to cause osseous changes in the sella turcica.

During the course of her gestation, the patient exhibited no clinical

change in her acromegaly. The laboratory findings were all within the accepted normal range for pregnancy—the serum protein-bound iodine level being elevated (59, 60); the tolerance to oral glucose being slightly impaired from the thirty-third week until the postpartum period, with glycosuria for several days after delivery; and the urinary excretion of formaldehydogenic and reducing steroids being increased above normal (61, 62). The urinary excretion of pregnanediol and 17-ketosteroids also followed a pattern consistent with gestation.

The serum protein-bound iodine and blood iodine levels are usually normal (63, 64), but may be increased (64, 65) during active acromegaly. It has been shown that the hypermetabolism of acromegaly, as indicated by the elevated BMR, occurs in the presence of a low or normal uptake of radioactive iodine; this suggests the existence of an extrathyroidal metabolic stimulus in acromegaly (66). In addition, the urinary excretion of formaldehydogenic and reducing steroids has been shown to be either normal (67) or increased (62, 67) in acromegaly, and it is known that approximately 33 per cent of active acromegalics exhibit an impairment of carbohydrate tolerance (6b). These findings, therefore, are present in both acromegaly and pregnancy, and in this instance can be explained on the basis of pregnancy alone. There is no suggestion from our studies that there is an additive effect in the presence of the two clinical conditions occurring in the same patient.

This case offers further evidence that the acromegalic female can conceive and carry to term. Pregnancy occurred twice and menstrual function subsequently returned to normal each time.

SUMMARY

The occurrence of pregnancy in an acromegalic female is uncommon. A review of the world literature has revealed 33 reported cases.

We have presented another, the thirty-fourth, together with a summary of the literature.

REFERENCES

1. Comte, L.: Contribution à l'étude de l'hypophyse humaine et de ses relations avec le corps thyroïde, *Beitr. z. path. Anat. u. z. allg. Path.* **23**: 90, 1898.
2. Erdheim, J., and Stumme, E.: Über die Schwangerschaftsveränderung der Hypophyse, *Beitr. z. path. Anat. u. z. allg. Path.* **46**: 1, 1909.
3. Chauta: quoted from Engelbach, W.: Endocrine Medicine. Springfield, Ill., Charles C Thomas, Publisher, 1932, vol. 3, p. 545.
4. Severinghaus, A. E.: Anterior hypophyseal cytology in relation to the reproductive hormones, *in* Sex and Internal Secretions, edited by E. Allen. Baltimore, The Williams & Wilkins Company, ed. 2, 1939, pp. 1045–1087.
5. Evans, H. M., and Simpson, M. E.: The effect of pregnancy on the anterior hy-

pophysis of the rat and cow as judged by the capacity of implants to produce precocious maturity, *Am. J. Physiol.* **89:** 379 (July) 1929.

6. Soffer, L. J.: Diseases of the Endocrine Glands. Philadelphia, Lea & Febiger, 1951, (*a*) p. 26, (*b*) p. 84.
7. Rea, R. L.: Neuro-Ophthalmology. St. Louis, The C. V. Mosby Company, 1938, pp. 275–276.
8. Lohlein: Die bitemporale Hemianopse der Schwangeren, *Monatschr. f. Geburtsh. u. Gynäk.* Bd.lxv, H.3–4 (quoted from Rea, (7)).
9. Comans and Beauvieux: (quoted from Soler, (34)).
10. McCurry, A. L.: The examination of the fields of vision in the last weeks of pregnancy, *Brit. J. Ophth.* **12:** 177 (Apr.) 1928.
11. Johns, J. P.: The Influence of pregnancy on the visual fields, *Am. J. Ophth.* **13:** 956 (Nov.) 1930.
12. Shimkin, N.: Contribution à l'étude de l'hemianopsie bitemporale gravidique, *Folia ophth. orient.* **1:** 90 (Nov.) 1932.
13. Williams, J. W.: Obstetrics, ed. 10, edited by N. J. Eastman. New York, Appleton-Century-Crofts, Inc., 1950, pp. 230–231.
14. Fruhinsholz, A.: Syndromes hypophysaires et gestation. Acromégalie gravidique, *Rev. méd. de Nancy* **50:** 255, 1922.
15. Marek, R.: Ueber einen Fall von Schwangerschaftsakromegalie, *Zentralbl. f. Gynäk.* **35:** 1612, 1911; **38:** 265, 1914 (quoted from Atkinson (47)).
16. Cushing, H.: The Pituitary Body and Its Disorders. Philadelphia, J. B. Lippincott Company, 1912.
17. Frankl, O.: Schwangerschafterblindung und Akromegalie, *Ztschr. f. d. ges. Anat.* =Abt. 2, *Ztschr. f. menschl. Vererb.- u. Konstitutionslehre* **11:** 166, 1925.
18. Hurxthal, L. M.; Hare, H. F.; Horrax, G.; and Poppen, J. L.: The treatment of acromegaly, *J. Clin. Endocrinol.* **9:** 126 (Feb.) 1949.
19. (*a*) Davidoff, L. M.: Studies in Acromegaly. III. The anamnesis and symptomatology in one hundred cases, *Endocrinology* **10:** 461 (Sept.-Oct.) 1926. (*b*) Davidoff, L. M.: Hyperpituitarism and hypopituitarism, *Bull. New York Acad. Med.* **16:** 227 (Apr.) 1940.
20. Putnam, T. J., and Davidoff, L. M.: Acromegaly, Chapter 42 *in* The Pituitary Gland, *Proc. A. Res. Nerv. & Mental Dis.* **17:** 714, 1938.
21. Engelbach, W.: Endocrine Medicine. Springfield, Ill., Charles C Thomas, Publisher, 1932, vol. 3, p. 545.
22. Henderson, W. R.: Sexual dysfunction in adenomas of the pituitary body, *Endocrinology* **15:** 111 (Mar.–Apr.) 1931.
23. Cagnetto, G.: Neuer Beitrag zum Studium der Akromegalie mit besonderer Berucksichtigung der Frage nach dem Zusammenhang der Akromegalie mit Hypophysengeschwulsten, *Arch. f. path. Anat.* **187:** 14, 1907.
24. Albright, F.: quoted from Reifenstein, E. C., Jr.: *in* Conference on Metabolic Aspects of Convalescence, edited by E. C. Reifenstein, Jr., Transactions of Fourteenth Meeting, Nov. 12–13, 1946, pp. 122–125. New York, Josiah Macy, Jr. Foundation.
25. Montes, F. G.: Sexual changes of acromegalic women, with report of cases, *Tokoginec. prâct.* (Madrid) **5:** 269 (Sept.) 1946.
26. Falta, W.: The Ductless Glandular Diseases, translated by M. K. Meyers. Philadelphia, P. Blakiston's Son & Co., 1915, pp. 235–282.

27. Zondek, H.: The Diseases of the Endocrine Glands, ed. 3. Baltimore, William Wood & Company, 1935, pp. 312–326.
28. Teel, H. M.: The effect of the growth principle of the hypophysis on the female genital tract: with the report of the hypertrophic changes in a case of acromegaly, *Endocrinology* **13:** 521 (Nov.–Dec.) 1929.
29. Pirie, J.: A case of acromegaly, *Lancet* **2:** 904 (Oct. 5) 1901.
30. Tandler, J., and Grosz, S.: Untersuchungen an Skobzen, *Wien. klin. Wchnschr.* **21:** 277, 1908 (quoted from Falta, (26)).
31. Creutzfeldt, H. G.: Ein Beitrag zur normalen und pathologischen Anatomie der Hypophysis cerebri des Menschen, *Jahrb. d. Hamb. Staatskrankenanst.* **13:** 273, 1908.
32. Goldberg, M. B., and Lisser, H.: Acromegaly: a consideration of its course and treatment. Report of four cases with autopsies, *J. Clin. Endocrinol.* **2:** 477 (Aug.) 1942.
33. Cushing, H., and Davidoff, L. M.: The Pathological Findings in Four Autopsied Cases of Acromegaly, with a Description of Their Significance. Monograph No. 22 of the Rockefeller Institute of Medical Research, New York, April 23, 1927.
34. Soler, J. P.: Acromegaly and pregnancy, *Medicina Clinica* **14:** 350 (May) 1950.
35. Klöppner, K.: Preservation of genital function; case of pregnancy in acromegaly of 9 years' duration, *Geburtsh. u. Frauenh.* **1:** 709 (Nov.) 1939.
36. Kalledey, L.: Schwangerschaft nach Akromegalie, *Zentralbl. f. Gynäk.* **37:** 1030, 1913.
37. Richter, A.: Akromegalie und Schwangerschaft. Inaug.-Diss., Berlin, 1940. *Zentralbl. f. Gynäk.* **64:** 1852, 1940.
38. Morgan, J.: Acromegaly with pregnancy, *Proc. Roy. Soc. Med.* **38:** 326 (Feb. 16) 1945.
39. Kemeny, E.: Akromegalie und Schwangerschaft, *Zentralbl. f. Gynäk.* **61:** 1967, 1937.
40. Cagnetto, G.: (quoted from Soler, (34)).
41. Stumme, E., and Hochenegg: (quoted from Soler, (34)).
42. Nedelkovitch, J.: (quoted from Soler, (34)).
43. Rosenberger: (quoted from Soler, (34)).
44. Teel, H. M.: (quoted from Soler, (34)).
45. Salle, V.: (quoted from Soler, (34)).
46. Albright, F.; Reifenstein, E. C., Jr.; Forbes, A. P., and Bartter, F. C.: Effect of estrogens in acromegaly, *in* Conference on Metabolic Aspects of Convalescence, edited by E. C. Reifenstein, Jr., Transactions of Fourteenth Meeting, Nov. 12–13, 1946, pp. 102–122. New York, Josiah Macy, Jr. Foundation.
47. Atkinson, F. R. B.: Acromegaly. London, John Bale, Sons & Danielsson, Ltd., 1932, pp. 47–48.
48. Garnier, S., and Santenoise: Une observation de manie aiguë chez une acromégalique, *Arch. de neurol.* 2S, **4:** 486, 1897.
49. Jackson, I.: Partial removal of acidophil adenoma of pituitary followed by two pregnancies, *Proc. Roy. Soc. Med.* **36:** 356 (May) 1943.
50. Bringle, C. G.: Pregnancy in an acromegalic following removal of pituitary tumor (case), *Memphis M. J.* **12:** 72 (May) 1937.
51. Hurxthal, L. M., and Dee, J. F.: Acromegaly, *Lahey Clin. Bull.* **3:** 196 (Jan.) 1944.
52. Starr, P., and Davis, L.: Endocrine studies of patients after subtotal hypophysectomy, *Ann. Surg.* **113:** 778 (May) 1941.

53. WEINSTEIN, A.: The response of acromegaly to deep roentgen-ray therapy: a case report, *Ann. Int. Med.* **13:** 715 (Oct.) 1939.
54. STURMA, J.: Rare case of twin pregnancy in patient with acromegaly, *Československ. gynaek.* **28:** 229, 1949.
55. SCHUR, M.: quoted from Atkinson, F. R. B.: Acromegaly, from a study of the literature, 1931–34, *Endocrinologie* **17:** 308, 1936.
56. LOWENBERG, S.: Clinical Endocrinology, ed. 2. Philadelphia, F. A. Davis Company, 1941, p. 156.
57. (*a*) SOMMERVILLE, I. F.; GOUGH, N., and MARRIAN, G. F.: The quantitative determination of small amounts of pregnanediol in human urine, *J. Endocrinol.* (British) **5:** 247 (Jan.) 1948. (*b*) VERLY, W. G.; SOMMERVILLE, I. F., and MARRIAN, G. F.: The quantitative determination and identification of pregnane-3α: 20α-diol in the urine of the pregnant rabbit, *Biochem. J.* **46:** 186, 1950.
58. (*a*) VENNING, E. H.: Gravimetric method for the determination of sodium pregnandiol glucuronidate (an excretion product of progesterone), *J. Biol. Chem.* **119:** 473 (July) 1937. (*b*) VENNING, E. H.: Further studies on the estimation of small amounts of sodium pregnanediol glucuronidate in urine, *J. Biol. Chem.* **126:** 595 (Dec.) 1938.
59. RAPPORT, R. L., and CURTIS, G. M.: The clinical significance of the blood iodine: a review, *J. Clin. Endocrinol.* **10:** 735 (July) 1950.
60. HEINEMANN, M.; JOHNSON, C. E., and MANN, E. B.: Serum precipitable iodine concentrations in pregnancy, *J. Clin. Invest.* **27:** 91 (Jan.) 1948.
61. LLOYD, C. W.; HUGHES, E. C.; LOBOTSKY, J., and RIENZO, J.: Some hormone studies during normal and toxemic pregnancy, (abstract) *J. Clin. Endocrinol.* **11:** 786 (July) 1951.
62. TALBOT, N. B.; WOOD, M. S.; WORCESTER, J.; CHRISTO, E.; CAMPBELL, A. M., and ZYGMUNTOWICZ, A. S.: Further observations on the urinary excretion of water-soluble corticosteroids by normal and abnormal subjects, *J. Clin. Endocrinol.* **11:** 1224 (Nov.) 1951.
63. CURTIS, G. M., and FERTMAN, M. B.: Blood iodine studies: the blood iodine in non-thyroid disease, *Arch. Surg.* **54:** 541 (May) 1947.
64. BECKER, D. V.; RALL, J. E.; PEACOCK, W., and RAWSON, R. W.: The effect of a thyrotrophic hormone preparation on the metabolism of radioiodine in euthyroid, hyperthyroid, and acromegalic individuals, *J. Clin. Invest.* **32:** 149 (Feb.) 1953.
65. PERKIN, H. J., and LAHEY, F. H.: The level of iodine in the blood, *Arch. Int. Med.* **65:** 882 (May) 1940.
66. MCCULLAGH, E. P.; GOLD, A., and MCKENDRY, J. B. R.: Radioactive iodine uptake in the hypermetabolism of acromegaly, *J. Clin. Endocrinol.* **10:** 687 (July) 1950.
67. VENNING, E. H., and BROWNE, J. S. L.: Excretion of glycogenic corticoids and of 17-ketosteroids in various endocrine and other disorders, *J. Clin. Endocrinol.* **7:** 79 (Feb.) 1947.

TEN YEARS' EXPERIENCE WITH RADIOACTIVE IODIDE*

EARLE M. CHAPMAN, M.D., FARAHE MALOOF, M.D., JORGE MAISTERRENA M.D. AND JORGE M. MARTIN, M.D.

The Thyroid Clinic of the Massachusetts General Hospital, Boston, Massachusetts

IT IS over twelve years since radioactive iodide was first used in the treatment of thyroid disease by Saul Hertz and it is just over ten years since we started its use as a therapeutic agent without the subsequent addition of ordinary iodide. In 1946, it was the fortune of one of us (E.M.C.) to present before this Association meeting in Chicago, the results of these early definitive studies (1). At that time we reported our experience in treating 45 patients with diffuse goiter and hyperthyroidism who had been treated with only I^{130}. We outlined then five points:

1. The use of radioactive iodide alone.
2. The definition of a single effective dose, the duration of its effect and the pattern of relapse, if any, of thyrotoxicosis.
3. The production of myxedema by a single dose.
4. The observation of the histologic changes in the same gland both before and after treatment.
5. The observation of the toxic effects of radioactive iodide.

These observations have been extended over a ten-year period and we now report to you on the fate of these first 45 treated patients (Table 1), as well as the biologic responses in others whom we have treated with I^{131} in the ten years to May 1953.

Since 1946 our *selection of cases* has been rather wide. After some uncertainties caused by fear of a carcinogenic effect, we lately have not always restricted the use of radioiodide so far as age is concerned. Because we found that the fetal uptake (2) of iodide begins in the fourth month, we have avoided its use in women pregnant beyond that time. Although our experience with nodular goiters is rather limited, we have formed an opin-

Received for publication July 2, 1953.

* Presented at the Annual Meeting of the American Goiter Association, Chicago, Ill., May 7–9, 1953.

This article will be included in the bound volume of the 1953 "Transactions of the American Goiter Association" published by Charles C Thomas, Publisher, which will be available for purchase early in 1954.

TABLE 1. THE 1953 FOLLOW-UP OF 45 PATIENTS WITH HYPERTHYROIDISM TREATED WITH RADIOACTIVE IODIDE 1943–46

30 responded: well in 1953	
9 responded: myxedematous in 1953	
1 in eighth year	
4 in fourth year	
4 in six months	
3 died	
2 euthyroid (gun shot, Ca of bronchus)	
1 toxic—pneumonia	
3 not seen	

ion that I^{131} is not to be used in persons with either a single or multiple nodular goiter. The reason for this is the high incidence of carcinoma in persons with a single nodule, and the fact that a multinodular goiter may diminish little in size after radiation therapy and may also harbor a cancer.

The clinical pattern illustrated in Figure 1 supports our opinion. The

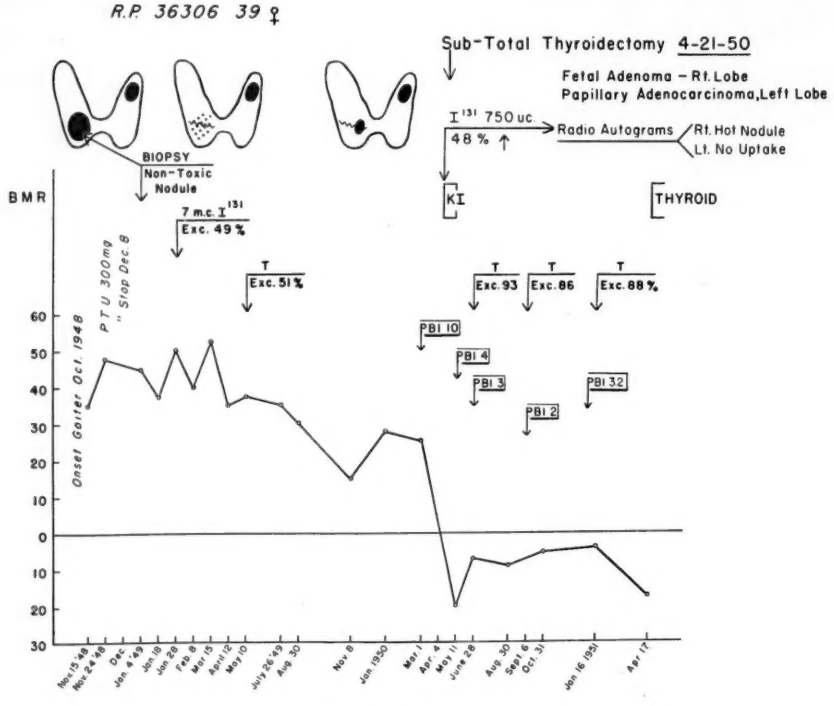


FIG. 1. (See text.)

patient had a nodule in each lobe of the thyroid and was thyrotoxic, but to persuade ourselves that she did not have a carcinoma we took a biopsy specimen from the nodule on the right—it was benign. Then we treated her with I^{131}. After a year she was better but still toxic and, as the nodule persisted in the left lobe of her thyroid, operative treatment was carried out. In the nodule on the left, papillary adenocarcinoma was found.

Next, let us consider the matter of I^{131} *dosage in hyperthyroidism* with diffuse goiter. This continues to be a matter of uncertainty. Sidney Werner has observed patients responding to tracer doses of 100 microcuries.

Other physicians are so eager to treat their patients that they give therapy doses of 2 to 10 millicuries every six to eight weeks. Our plan has been to estimate the size of the goiter as well as we can by clinical judgment. Then, from a background of experience in recognizing the evidence of overtreatment and undertreatment, we have arrived at the dosage figure of 160 microcuries of I^{131} per estimated gram of thyroid. This is based on an assumed average 48-hour retention of 70 per cent of the previous tracer dose that serves as the guide for therapy. After treating the patient we usually allow from six to twelve months to elapse before considering a second dose. Factors for second doses in previously radiated tissues may be quite different and on this point we are clouded in ignorance. It has been our experience that patients resistant to therapy require usually the same amount or even more for the second dose.

RESULTS

From 1946 until now we have treated 400 additional patients with I^{131}.

In Table 2 it may be seen that 5 patients were operated on after a partial response. These were mostly instances of nodular goiter which persisted with a large mass causing pressure symptoms; thus, operation was in-

TABLE 2. RESULTS IN 465 PATIENTS TREATED WITH RADIOACTIVE IODIDE

I^{130}		65 cases
I^{131} (August 1946–August 1952)		400 cases
305 responded	1 dose	
40 responded	2 doses	
8 responded	3 doses	
2 responded	4 doses	
355		
19 better but toxic six months after treatment		
5 operated on after response		
21 died since treatment, from other causes. (10 autopsies)		
400		

dicated. Of the 21 who died (10 autopsies), none showed primary carcinoma of the thyroid, although 2 died of cancer in other areas and showed metastases to the thyroid.

TABLE 3. RESULTS IN 400 PATIENTS TREATED WITH I^{131}

August 1946–August 1952

Radiation—97% delivered in	30 days
Radiation sickness	0
Average interval before BMR became normal	2 mos.
Average interval before occurrence of myxedema	4 mos.
Incidence of post-treatment myxedema	8%
Recurrence of hyperthyroidism	0.01%

From Table 3 it will be noted that the average interval before the basal metabolism became normal was two months. The average interval before the appearance of myxedema was four months. Thirty-two or 8 per cent of the patients became myxedematous. Of these, only 1 had two doses of I^{131} and only 1 had an operation previously for hyperthyroidism. The average dose that caused the myxedema was about 8 millicuries and the average excretion of I^{131} in forty-eight hours was 22 per cent. Myxedema was usually established by the fourth month after therapy. In these patients the error seems to have been in an over-estimate of the gland size in calculating the dosage. In 3 persons myxedema developed after doses of 6 millicuries—about the lowest that we give for hyperthyroidism. The largest dose causing unintentional myxedema was 10 millicuries.

In Table 3 it will be noted that the incidence of recurrence is given as 0.01 per cent. This, of course, represents less than 1 patient and is only a numerical way of expressing our awareness of the problem. Although we have not seen recurrence after the patient has remained in a euthyroid state for a matter of several months, we have seen the indices of function drop to normal levels following treatment but soon rise again in association with a chronic state of persistent thyrotoxicosis because of an inadequate dose. We do not classify these as cases of recurrent disease but rather as cases of persistent disease.

Figure 2 illustrates three important points: 1) three days after an intravenous pyelogram the excretion of radioactivity in forty-eight hours was increased by 19 per cent; seven days later it was increased by only 7 per cent, 2) the response was perhaps rather slow over a period of about four to six months, and 3) the patient had co-existent bursitis of the right shoulder; throughout the period of response the shoulder improved to the point of complete use and the calcification disappeared, as was proved by repeated

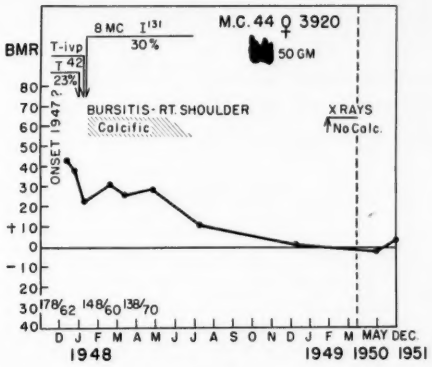


FIG. 2. (See text.)

x-ray examination. It is known that the calcium metabolism is in a state of flux during hyperthyroidism, a fact which further supports this observation. Last year a number of patients with bursitis of the shoulder in association with thyroid disease were reported (3) at the meeting of this Association. We have also seen bursitis in the presence of hyperthyroidism in about 20 patients.

Figure 3 illustrates the failure of the thyroid to regenerate two years

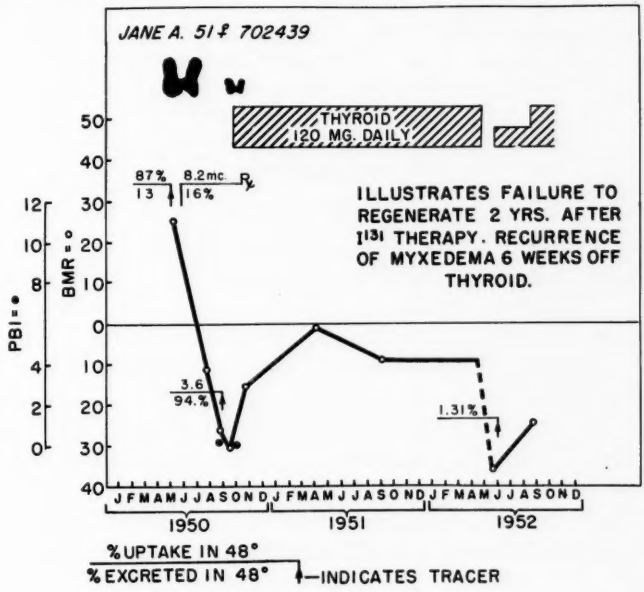

JANE A. 51 ♀ 702439
THYROID
120 MG. DAILY
87%
13
8.2mc.
16%
ILLUSTRATES FAILURE TO REGENERATE 2 YRS. AFTER I131 THERAPY. RECURRENCE OF MYXEDEMA 6 WEEKS OFF THYROID.
PBI = •
BMR = o
3.6
94.%
1.31%
J F M A M J J A S O N D J F M A M J J A S O N D J F M A M J J A S O N D
1950
1951
1952
%UPTAKE IN 48°
%EXCRETED IN 48°
—INDICATES TRACER

FIG. 3. (See text.)

after I^{131} therapy and clearly shows the recurrence of myxedema six weeks after omission of thyroid treatment. The indices of function as measured by the tracer uptake and the basal metabolic rate quickly dropped to a low level when thyroid was omitted; likewise the patient quickly became myxedematous. With the resumption of thyroid treatment she became euthyroid.

Figure 4 shows the reverse of the foregoing phenomenon. Here we see

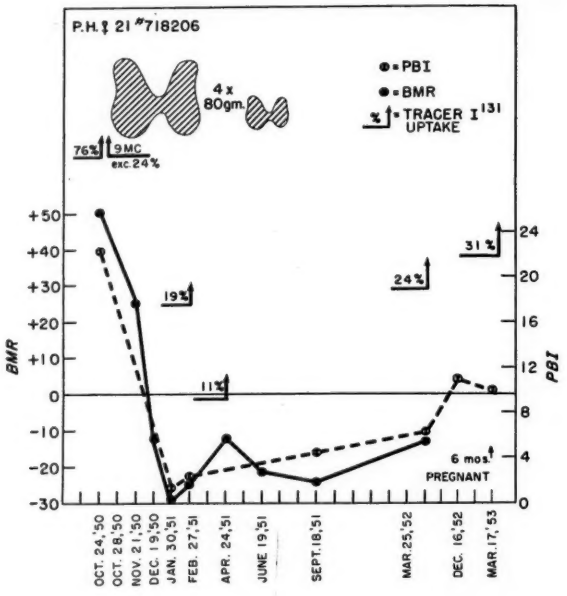


FIG. 4. (See text.)

the patient becoming myxedematous but by the exercise of patience and witholding of treatment, in fact by exercising a good deal of restraint in avoiding treatment, this patient's indices gradually rose to the normal level over a period of about a year, and the patient felt well. Late in 1952 she became pregnant. At this time the tracer uptake was 24 per cent and the PBI concentration rose to 11γ per 100 ml. When these determinations were repeated in March 1953, the value for PBI was about 10γ per 100 ml. and the tracer uptake had only risen to 31 per cent. The physiologic rise in the serum protein-bound iodine level during pregnancy evidently is not paralleled by an expected rise in the tracer uptake. This poses an interesting problem in the physiology of the thyroid cell during pregnancy.

Figure 5 illustrates the fact that the patient continued in a state of

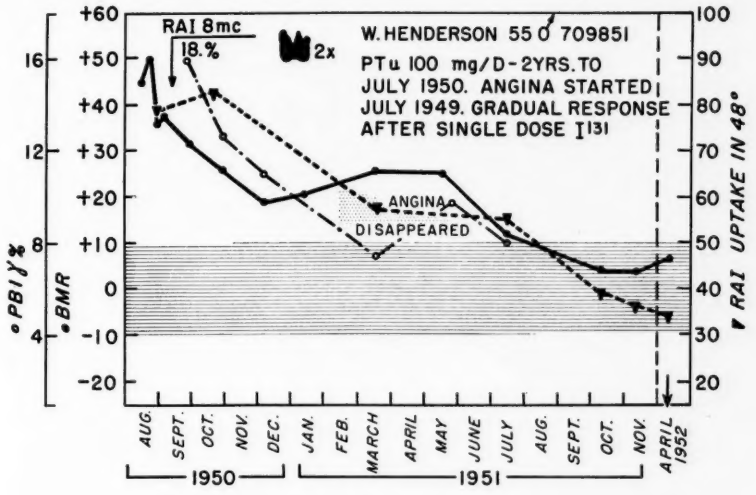


FIG. 5. (See text.)

thyrotoxicosis while receiving propylthiouracil therapy; indeed this man's angina developed while under this treatment, a clinical situation we have seen in several patients. He then received a single dose of 8 millicuries of radioactive iodide, of which he excreted 18 per cent in forty-eight hours. Thereafter there was a gradual decline in the indices of function over the following year. Late in this period his angina disappeared. Finally in mid-1951 the PBI and tracer uptakes showed normal values and the patient continued well. This gradual response over the period of a year has been observed by us in a number of instances, so again we point out that the response to radioactive iodide is a gradual process and that one must be patient in awaiting this response and thus avoid the unnecessary use of second doses, which may contribute to the high incidence of myxedema as noted in other reports.

Figure 6 illustrates the continuing response over a long period of time and one wonders whether this response to a single dose of radioactive iodide (a rather small amount—8 millicuries—given in 1948) represents injury to the cell that has caused latent or slow changes, or whether the gradual decline in function is due to avascularity from fibrosis. This woman was an older person, aged 63 at the time of her first treatment, and perhaps at her age thyroid function was naturally declining. It raises doubt as to the wisdom of administering larger doses (250 microcuries per estimated gram of thyroid) in people above the age of 40, as recommended by others; with such doses, in time there may be a greater number of patients with myxedema.

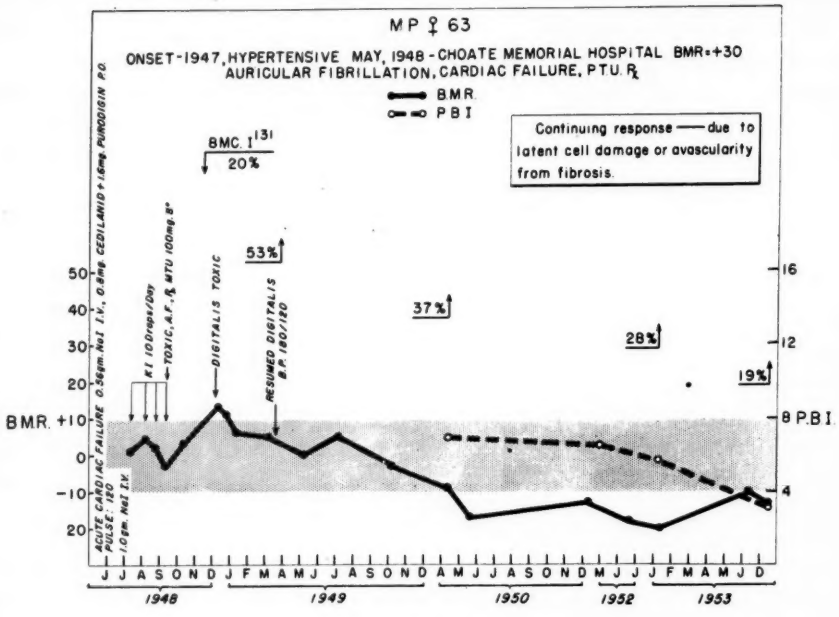

MP ♀ 63
ONSET-1947, HYPERTENSIVE MAY, 1948 - CHOATE MEMORIAL HOSPITAL BMR+30
AURICULAR FIBRILLATION, CARDIAC FAILURE, P.T.U. Rx
BMR
PBI
Continuing response — due to latent cell damage or avascularity from fibrosis.
BMC. I131 20%
53%
37%
28%
19%
DIGITALIS TOXIC
RESUMED DIGITALIS
BMR. +10
8 P.B.I.
J J A S O N D J F M A M J J A S O N D J F M A M J J A S O N D M J J J F M A M J D
1948
1949
1950
1952
1953

FIG. 6. (See text.)

Figure 7 illustrates an interesting point that we have seen in a number of cases and that is the dissociation of the indices of function after the first treatment, while the patient remains toxic. This patient was given 10 millicuries of I^{131} early in 1949 but continued toxic and was obviously toxic while the tracer uptakes were only 38 and 46 per cent. Following a second dose of 7 millicuries in the spring of 1950 the indices of function as measured by the PBI and BMR gradually declined to normal over a period of almost a year and yet the tracer uptake remained about the same.

Table 4 shows the values for tracer uptakes of I^{131} and the PBI levels

TABLE 4. TRACER UPTAKES OF I^{131} AND PBI LEVELS AFTER TREATMENT WITH I^{131}

	Tracer uptake of I^{131} (48° ↑ —%)	PBI (γ 100 ml.)
Euthyroid after ℞ (Average—50 cases)	33.4 (Range 20–50)	5.7 (Range 3.1–7.8)
Toxic after ℞ (Average—10 cases)	47.7 (Range 33–59)	10.9 (Range 7.4–14.3)
Normal	20–55	3.5–8.0

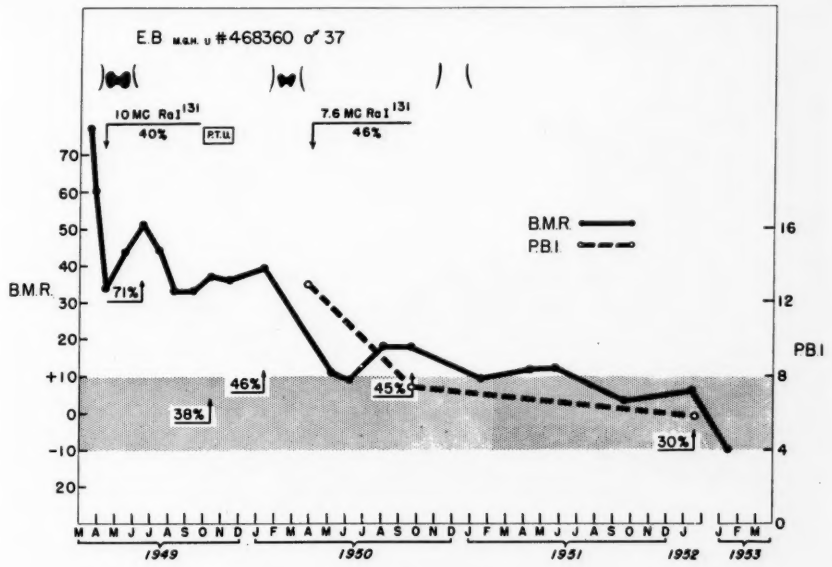


FIG. 7. (See text.)

after treatment with I^{131} and summarizes our experience in regard to this matter. In 50 cases the average thyroidal uptake of tracer doses was 33 per cent in forty-eight hours; the average PBI level was 5.7 γ per 100 ml. These patients were all clinically euthyroid. However, in a group of 10 patients who were still toxic after the first treatment dose, the average uptake of a tracer dose was 47 per cent and the PBI level was high, averaging 10.9 gamma per 100 ml. We are puzzled to explain this low thyroidal uptake of radioactive iodine at a time when the thyroid cells seemed to be producing more than a normal amount of protein-bound iodine. Perhaps the physiologists can help us.

Figure 8 shows a histologic section of thyroid tissue removed eight years after radiation therapy with I^{131}. Note the bizarre nuclear forms. We have obtained tissue from the thyroids of 44 patients who had previously been treated with radioactive iodide and in the examination of these tissues we have not seen any evidence of carcinoma. However, we have observed fibrosis, infiltration of lymphocytes and these bizarre nuclear forms that Brown Dobyns and the rest of us are reporting in a separate paper (4).

CONCLUSIONS

1. Radioactive iodide is an effective agent in the control of hyperthyroidism caused by a diffusely hyperplastic thyroid.

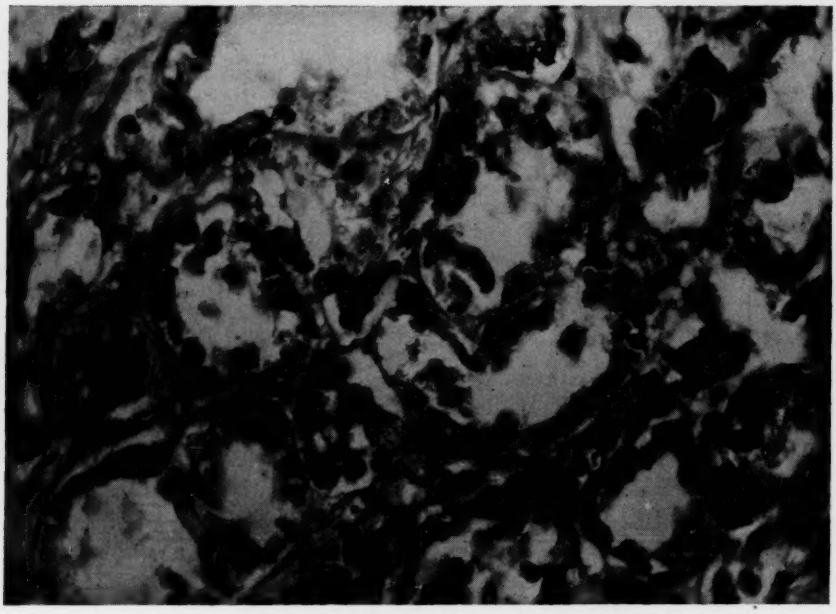


FIG. 8. Histologic section showing bizarre nuclear forms in thyroid tissue removed eight years after treatment with radioactive iodide.

2. The biologic response to this form of radiation is gradual and patients may continue to respond over several months. Indeed, myxedema has appeared many years after the original cell injury.

3. Following radiation therapy with I^{131}, studies by means of thyroidal tracer uptakes of radioactive iodide, serum protein-bound iodine determinations and basal metabolic rates, reveal several patterns. The patient may become myxedematous, euthyroid, or continue in persistent hyperthyroidism with the usual indices. However, we have observed dissociation of the indices of function in two groups: first, in several apparently euthyroid patients with tracer uptakes under 20 per cent, serum protein-bound iodine levels less than 3 γ per 100 ml., and basal metabolic rates above -20 per cent; and second, in those patients who are toxic with a high protein-bound iodine level and a high basal metabolic rate but with a normal thyroidal uptake of radioactive iodide.

4. I^{131} radiation produces fibrosis and cellular damage in the thyroid, resulting in bizarre nuclear forms; yet some of the remaining follicles appear hyperplastic. Histologic sections from 44 thyroids studied after radiation revealed no evidence of malignancy.

REFERENCES

1. CHAPMAN, E. M.: Treatment of Graves' disease with radioactive iodine, *Tr. Am. A. Study Goiter* pp. 74–78, 1942–1946.
2. CHAPMAN, E. M.; CORNER, G. W., JR.; ROBINSON, D., and EVANS, R. D.: The collection of radioactive iodine by the human fetal thyroid, *J. Clin. Endocrinol.* **8**: 717, 1948.
3. SKILLERN, P. G.: The association of periarthritis of the shoulder with hyperthyroidism, *Tr. Am. Goiter A.* p. 100, 1952.
4. DOBYNS, B. M.; VICKERY, A.; MALOOF, F., and CHAPMAN, E. M.: Functional and histologic effects of therapeutic doses of radioactive iodine on the thyroid of man, *J. Clin. Endocrinol. & Metab.* **13**: 548, 1953.

ANTIGOITROGENIC AND CALORIGENIC ASSAY OF THYROGLOBULIN, DESICCATED THYROID AND *l*-THYROXINE BY DIFFERENT ROUTES OF ADMINISTRATION IN RATS

R. L. KROC, PH.D., G. E. PHILLIPS, PH.D., N. R. STASILLI AND S. MALAMENT, M.S.

The Research Division of Warner-Chilcott Laboratories, Morris Plains, New Jersey

INTRODUCTION

THE physiologic basis for the agreement between the clinical effectiveness of various thyroid preparations and their potency as assayed by the U.S.P. total iodine method has been well reviewed by Means (1). From assays in myxedematous patients, Salter, Lerman and Means (2, 3) concluded that the calorigenic activity of thyroid is related to its total organic iodine and not to its thyroxine iodine. In all of their assays of desiccated thyroid the response was four or five times greater than expected on the basis of its thyroxine content.

Assays in rats by Gaddum (4) and Frieden *et al.* (5, 6), in guinea pigs by White, McGinty, Anderson and White (7), and in amphibia by Hamilton, Albert and Power (8) showed similar results. These investigators observed that natural thyroid proteins show more thyroxine-like activity than can be accounted for from their thyroxine content, even assuming that *dl*-thyroxine possesses half the activity of *l*-thyroxine. With this assumption other investigators reported agreement between the activities of thyroid preparations and *dl*-thyroxine in terms of *l*-thyroxine content (9, 10). On the other hand, evidence that the activity of thyroid proteins may not be correlated with either total iodine or thyroxine content was reported by Meyer and Wertz (11).

The basic problem of comparing materials of radically different chemical nature and molecular size, *e.g.*, desiccated thyroid or thyroglobulin versus thyroxine, was accentuated by differences in solubility and probably the

Received for publication July 14, 1953.

*Presented at the Annual Meeting of the American Goiter Association, Chicago, Ill., May 7–9, 1953.

This article will be included in the bound volume of the 1953 "Transactions of the American Goiter Association" published by Charles C Thomas, Publisher, which will be available for purchase early in 1954.

rates of absorption and utilization. Desiccated thyroid could not be administered parenterally except as a suspension (5, 6). To simplify this aspect of the problem it was desirable to prepare thyroglobulin in a relatively purified, soluble or undenatured form. Since the active principle in thyroid is presumably in the levo form, comparisons could be made not only with solutions of *dl*-thyroxine, but also with solutions of *l*-thyroxine sodium and *l*-triiodothyronine. Cortell (12) made such a comparison between parenterally administered solutions by the antigoitrogenic method. She observed that soluble thyroglobulin was six to eight times more active than crystalline thyroxine per microgram of thyroxine iodine. We (13) assayed the same thyroglobulin solution calorigenically against the same make of crystalline thyroxine as a standard. Tests over a wide range of dosages in both normal and thyroidectomized rats confirmed Dr. Cortell's conclusion. When sodium *l*-thyroxine became available we anticipated that it should be more active than crystalline thyroxine because the latter was prepared from thyroids by alkaline hydrolysis and was presumably racemized in the process to the less active *dl*-mixture.

The present study is part of a continuing program of thyroid research seeking an explanation for the high activity of thyroglobulin. As one aspect of that problem, this study compares the goiter-prevention and calorigenic activities of another preparation of soluble thyroglobulin (made up in larger quantity and more completely analyzed and characterized as to purity) with *l*-thyroxine sodium and commercial thyroid products by different routes of administration. The results confirm the previous reports of Cortell (12) and Kroc and Stasilli (13) and suggest that rate of absorption is not the explanation for the high activity of thyroglobulin in terms of "thyroxine" iodine.

MATERIALS AND METHODS

Animals: Albino rats of our own colony, originally derived from the Wistar strain, were used—males weighing 250–300 grams, 130–150 days of age, for the calorigenic (BMR) tests; females weighing 150–200 grams, for the goiter-prevention assays. From the time of weaning, all of the rats were maintained on Rockland Laboratory Rat Diet. Animal room temperature was maintained at $74 \pm 3°$ F.

Calorigenic assay: Two to three weeks before the basal metabolic rate (BMR) tests were started, the males were started on a diet of two parts by weight of ground whole wheat and one part whole milk powder plus sodium chloride, 2 per cent. This diet was used in order to conform with earlier experiments (13) in which a high calcium diet was used to control the incidence of tetany following thyroidectomy. The daily 5-hour afternoon feeding, 19-hour fasting, schedule employed by Barker (14) was followed for the 2–3 week conditioning period and the succeeding five days when daily BMR tests were run. Our observations confirmed Barker's finding that the body weight drops at the start of the regimen and then become stabilized close to the original weight. The rats were placed in metabolic chambers in the morning thirty minutes before oxygen consumption read-

ings were made at ten-minute intervals, from 16 to 17.5 hours after food was made unavailable in a specially designed cage. Twelve metabolism chambers were housed in a constant-temperature, forced-air circulation, cabinet maintained at 29 ± 0.5°C. Closed-circuit units of the Benedict (15) type were used. All parts of the units, water-sealed chambers, natron CO_2 absorption tubes, oil-sealed pumps and spirometer O_2 reservoirs, were in the cabinet. The four lowest of six 10-minute O_2 consumption readings for each rat were averaged, corrected to standard temperature and pressure and calculated on a body-weight basis, to obtain the "basal" rate for that day. The rates for the first two days were averaged to obtain the pre-treatment BMR level. Preparations were administered subcutaneously (s.c.), intravenously (i.v.), intraperitoneally (i.p.) or orally (p.o.) (stomach tube) once daily for three days after the rats were removed from the chambers on the second to fourth days and before food was made available. The BMR on the fifth day, approximately seventy and twenty-two hours respectively after the first and last doses, was taken as the post-treatment rate for comparison with the pre-treatment BMR. Previous experience (16) had demonstrated that most of the rats reached their peak response on this day and that the rates returned to normal or slightly subnormal levels by five days after the last dose.

Antigoitrogenic assay: Following the method of Dempsey and Astwood (17), female rats were given a 0.1 per cent solution of thiouracil in tap water as their drinking water for fourteen days, during which the test preparations were administered subcutaneously or by stomach tube once daily. The denatured or insoluble preparations given orally were ground in a mortar, followed by slow addition (with continued grinding) of 1 per cent aqueous gum tragacanth. This method of suspension was also employed for oral administration in the calorigenic assays. On the fifteenth day the dosage groups and concomitant thiouracil and untreated normal control groups of 10 rats each were weighed, sacrificed, and the thyroids dissected on wet filter paper and weighed to the nearest 0.1 mg.

Preparations assayed: Table 1 lists the total and "thyroxine" iodine content of each preparation, and the methods of analysis that were followed. The sample of *l*-thyroxine sodium pentahydrate[1] was labeled *l*-thyroxine sodium, 87.4%, H_2O 9.1%. The soluble thyroglobulin (preparation #91921) was prepared by sodium chloride extraction of ground pork thyroids at a pH of 8. Thyroglobulin was precipitated by half-saturation of the filtrate with ammonium sulphate. The precipitate was removed by centrifugation and dialyzed against distilled water. This process of precipitation and dialysis was repeated several times and the final thyroglobulin solution was dialyzed against several changes of physiologic saline. The clear, filtered extract was then lyophilized in vials, so that addition of 4 ml. of distilled water reconstituted a solution isosmotic with physiologic saline. In addition to total and thyroxine iodine determinations, the following analyses were made on the lyophilized material: total nitrogen by the Kjeldahl method, 11.47 per cent; ash, 24.64 per cent; inorganic iodine by U.S.P. XIV, absent.

Paper electrophoresis tests of the thyroglobulin solution showed that the material moved largely in a single band. Robbins and Rall (18) made similar observations by the paper method on this preparation. As reported by them, Dr. Mary Peterman found at least 75 per cent of one component, presumably thyroglobulin, and two or three small components by ultracentrifugal analysis. Becker (19) independently made similar observations on this preparation. He obtained a major component which was 75–85 per

[1] We are indebted to Dr. Carl H. Cunov of Smith, Kline and French Laboratories for a supply of *l*-thyroxine sodium pentahydrate.

TABLE 1. TOTAL AND THYROXINE IODINE ANALYSES OF PREPARATIONS USED

Preparation	Total iodine* %	Thyroxine iodine† %	Thyroxine iodine ratio
l-Thyroxine sodium pentahydrate	55.5	55.5‡	1.0000
Soluble thyroglobulin	0.773	0.212	0.2743
Thyroglobulin, Product A	0.84	0.245	0.2917
Desiccated thyroid USP, Product B	0.20	0.062§	0.31
Desiccated thyroid, Product C	0.69	0.19	0.2754

* USP XIV.

† Blau, 1935 (20).

‡ All iodine assumed to be in thyroxine combination.

§ Calculated from analyses made on sample freed from diluents.

cent of the total, and a sedimentation constant characteristic of thyroglobulin. There was a small amount of component with a higher sedimentation constant and there was a fraction which was inhomogeneous ultracentrifugally, with a slower rate of sedimentation than the thyroglobulin. Becker also succeeded in immunizing rabbits to a sample of thyroglobulin, using subcutaneous injection in Freund's adjuvant. He found at least three antigenic components in the thyroglobulin. One component, presumably thyroglobulin, was in the highest quantity and gave rise to a relatively large amount of precipitin antibody (0.7 mg. of antibody nitrogen per ml. of serum). The other two components were much less antigenic.

Product "A", thyroglobulin,[2] was prepared by alkaline saline extraction and by centrifugation and filtration to remove cells, connective tissue and most of the fat. Proteins were then precipitated from the supernatant solution by heating and acidification. Finally adsorbed fats and combined lipids were removed by repeated solvent extraction of the precipitate, which was then dried, ground and sieved to a fine powder.

Information is not available, nor is it specified in U.S.P. XIV, on the exact method for manufacture of desiccated thyroid (Products "B" and "C").

Dosages for all preparations were based on total iodine as determined by U.S.P. XIV analysis. This was considered a more accurate and conservative basis because the U.S.P. method is a highly standardized procedure, whereas the methods vary for determining iodine in "thyroxine" combination. All "thyroxine" iodine analyses given in this paper were carried out by the Blau method (20).

RESULTS

Antigoitrogenic assay—controls. Table 2 shows the variation in thyroid weights for groups of 10 normal and thiouracil control rats. One group of each control type was observed concomitantly with each series of dosage groups of 10 rats each. Because of proximity in time of scheduled autopsy, normal controls were omitted in two dosage series. The thiouracil controls

[2] A supply of Proloid® concentrate without diluents was provided through the cooperation of Mr. J. V. Battista, Warner-Chilcott Laboratories.

TABLE 2. THYROID WEIGHTS OF NORMAL AND THIOURACIL-TREATED (0.1% IN DRINKING WATER) FEMALE RATS, BY GROUPS OF 10

Groups	Av. thyroid wt. (mg./100 Gm. body wt.)	±S.E.
Thiouracil	13.2	0.9
	13.2	1.0
	14.2	0.7
	16.2	0.8
	15.4	0.7
	12.9	0.7
	13.0	1.0
	$m \pm$S.E. $= 14.0 \pm 0.5$	
Normal	4.8	0.2
	4.9	0.3
	5.6	0.3
	5.7	0.3
	4.8	0.2
	$m \pm$S.E. $= 5.2 \pm 0.2$	

served as a check on the drinking water solution which was made up fresh every two or three days. The controls also served to measure the consistency with which the thyroids, goitrous and normal, were dissected free of surrounding tissue. Dissection of all control and dosage groups was performed by the same individual.

Antigoitrogenic assay of l-thyroxine and soluble thyroglobulin by subcutaneous and oral routes. Table 3 and Figure 1 summarize the results. Both preparations were given as solutions once daily for fourteen days, by

TABLE 3. ANTIGOITROGENIC ASSAY OF *l*-THYROXINE AND SOLUBLE THYROGLOBULIN: ORAL AND SUBCUTANEOUS ADMINISTRATION

Dose* (μg. iodine per day)	Oral *l*-thyroxine			Oral thyroglobulin			S.C. *l*-thyroxine			S.C. thyroglobulin		
	No. of rats	Thyroid wt. (mg./100 Gm.)	±S.E.	No. of rats	Thyroid wt. (mg./100 Gm.)	±S.E.	No. of rats	Thyroid wt. (mg./100 Gm.)	±S.E.	No. of rats	Thyroid wt. (mg./100 Gm.)	±S.E.
0.5	10	16.2	1.2	10	14.2	1.0	10	14.5	0.7	9	14.8	0.7
1.0	10	13.8	0.7	10	11.9	0.8	10	12.5	1.2	7	11.3	1.0
1.5	—	—	—	—	—	—	9	9.3	1.3	10	10.7	1.7
2.0	9	12.2	0.9	20	10.3	0.9	10	4.5	0.3	18	5.4	0.5
3.0	10	9.6	0.7	10	6.5	0.9	—	—	—	—	—	—
4.0	10	7.5	1.3	10	5.2	0.4	—	—	—	—	—	—
6.0	10	4.3	0.1	9	4.4	0.3	—	—	—	—	—	—

* See Table 2 for normal and thiouracil controls.

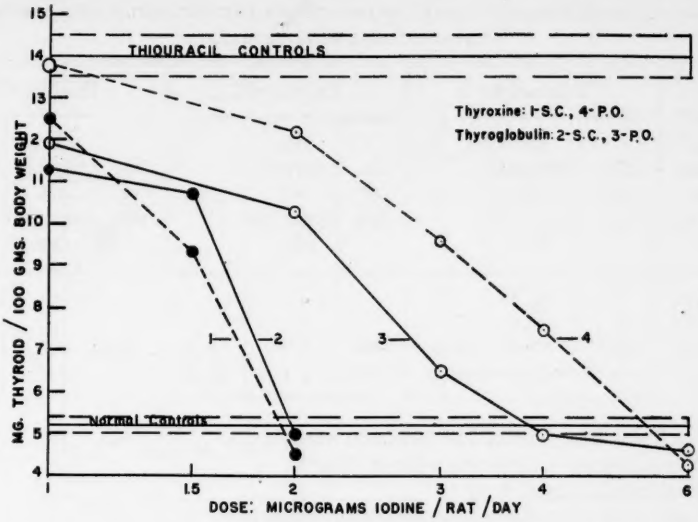

THIOURACIL CONTROLS
Thyroxine: 1-S.C., 4-P.O.
Thyroglobulin: 2-S.C., 3-P.O.
MG. THYROID / 100 GMS. BODY WEIGHT
Normal Controls
DOSE: MICROGRAMS IODINE / RAT / DAY

FIG. 1. Antigoitrogenic assay of *l*-thyroxine and soluble thyroglobulin: subcutaneous and oral administration.

injection or stomach tube. Material administered by the parenteral route was distinctly more active than when given by the oral route. Compared with *l*-thyroxine s.c. on a total iodine basis at the $p = .05$ level of significance—soluble thyroglobulin s.c. was not significantly different in activity; *l*-thyroxine oral, and soluble thyroglobulin oral were significantly lower in activity.

With the number of animals used, the difference between soluble thyroglobulin and *l*-thyroxine oral was borderline at $p = .05$ and therefore could not be considered significant.

Antigoitrogenic assay of thyroid products—oral administration. Table 4 and Figure 2 show the data obtained following stomach-tube administration of suspensions of denatured thyroglobulin and desiccated thyroid. All three products were nearly equally active per microgram of total iodine. The small differences are not significant at $p = .05$. When the products, tested orally, were compared with *l*-thyroxine and soluble thyroglobulin tested subcutaneously, the difference was not found to be significant with the number of rats used.

Calorigenic assay of l-thyroxine and thyroid preparations—subcutaneous and oral administration. Table 6 and Figure 3 summarize the experimental and control data. *L*-thyroxine and soluble thyroglobulin were equal to each other in activity on a total iodine basis. However, the oral activity

TABLE 4. ANTIGOITROGENIC ASSAY OF DENATURED THYROGLOBULIN AND DESICCATED THYROID: ORAL ADMINISTRATION

Dose* (μg. iodine per rat/day)	Product A†			Product B‡			Product C§		
	No. of rats	Av. thyroid wt. (mg./100 Gm.)	±S.E.	No. of rats	Av. thyroid wt. (mg./100 Gm.)	±S.E.	No. of rats	Av. thyroid wt. (mg./100 Gm.)	±S.E.
1.0	9	13.2	1.4	—	—	—	—	—	—
1.5	10	8.1	0.9	—	—	—	—	—	—
2.0	20	7.5	0.8	10	7.2	1.2	10	8.5	1.3
3.0	9	3.5	0.2	9	4.6	0.6	10	4.6	0.4

* See Table 2 for normal and thiouracil controls.
† Thyroglobulin concentrate without diluents.
‡ Desiccated thyroid, U.S.P.
§ Desiccated thyroid concentrate without diluents.

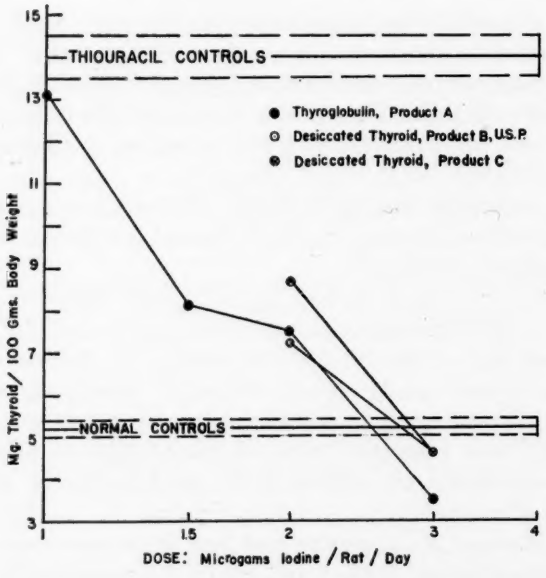


FIG. 2. Antigoitrogenic assay of denatured thyroglobulin and desiccated thyroid: oral administration.

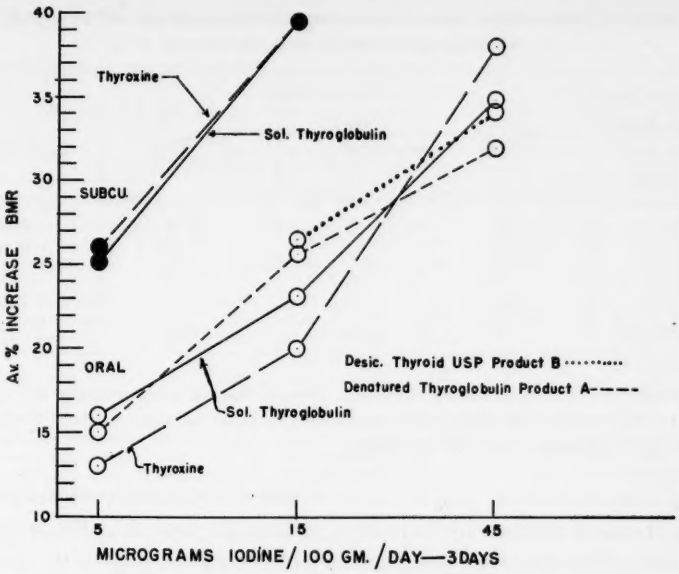


FIG. 3. Calorigenic assay of *l*-thyroxine and thyroid preparations: subcutaneous and oral administration.

of each preparation was significantly lower than its subcutaneous activity at $p = .05$. The denatured thyroid products, thyroglobulin and desiccated thyroid "B," were not significantly different from each other or from *l*-thyroxine and soluble thyroglobulin orally. By this calorigenic method of assay, therefore, no difference was observed between the activities of denatured versus undenatured thyroid protein.

Calorigenic tests of soluble thyroglobulin by intravenous and intraperitoneal administration. Intravenous injections by tail vein were performed by Dr. C. C. Scott. The rats were dosed once daily for three days as in the other calorigenic assays. From the data in Table 5, soluble thyroglobulin appears to be equally active by both routes and, referring to Table 6 and Figure 3, apparently at least as active as by subcutaneous administration. Because of the small numbers of animals, however, the data may be regarded as only qualitative. The similarity of response following i.v., i.p. and s.c. administration and the lack of response to a control hog-protein extract suggest that nonspecific calorigenic agents or effects were not responsible for the metabolic increases following i.v. administration. To our knowledge, this is the first report on the calorigenic effects of intravenously administered thyroglobulin.

Relative activities of l-thyroxine and thyroid preparations by different

TABLE 5. CALORIGENIC ASSAY OF SOLUBLE THYROGLOBULIN: INTRAVENOUS AND INTRAPERITONEAL ADMINISTRATION

Dose (μg. iodine/ 100 Gm. body wt. per day) for 3 days	Route	No. of rats	Av. % increase in BMR	±S.E.
5.0	I.P.	5	33.4	4.0
15.0	I.P.	7	37.7	0.9
5.0	I.V.	6	29.5	3.2
15.0	I.V.	6	48.3	7.6
Controls*	I.V.	4	−8.5	—

* Received hog ovary extract containing 250 guinea pig units relaxin/ml. (30, 31). Dose: 0.43 ml./rat/day for three days, equivalent in total nitrogen content to that contained in the highest dose of thyroglobulin.

routes of administration. Table 7 summarizes the data of both methods of assay in terms of total and "thyroxine" iodine. Endpoints in the antigoitrogenic assay represent the dose required for complete inhibition of goiter. For the calorigenic assay the endpoint was taken as the dose required for a 30 per cent increase in BMR. Relative activities were calculated by assigning the value 100 to the activity of *l*-thyroxine administered subcutaneously.

DISCUSSION

The validity of the relative potency estimates (Table 7) is dependent upon the accuracy of the assay methods employed and the chemical

TABLE 6. CALORIGENIC ASSAY OF *l*-THYROXINE AND THYROID PREPARATIONS: SUBCUTANEOUS AND ORAL ADMINISTRATION

Preparation	Route	Dosage: μg. iodine/100 Gm. body wt./day for 3 days								
		5 μg.			15 μg.			45 μg.		
		No. of rats	Av. % incr. in BMR	±S.E.	No. of rats	Av. % incr. in BMR	±S.E.	No. of rats	Av. % incr. in BMR	±S.E.
l-Thyroxine	S.C.	16	26.1	2.6	15	39.5	3.3	—	—	—
Soluble thyroglobulin	S.C.	18	25.2	2.7	17	39.4	3.0	—	—	—
Thyroglobulin, Product A	P.O.	18	14.9	3.1	75	25.7	1.6	59	32.0	1.9
Des. thyroid, USP, Product B	P.O.	—	—	—	13	26.4	2.3	16	34.1	2.7
Soluble thyroglobulin	P.O.	16	15.9	2.3	17	23.2	2.3	12	34.6	3.2
l-Thyroxine	P.O.	17	13.1	2.3	16	20.1	1.7	12	38.0	2.8
Controls, treated	P.O.	(1% gum tragacanth—1 ml./100 Gm./day, for 3 days)						19	−4.9	—
Controls, untreated	—							23	−9.4	—
Controls, combined	—							42	−7.4	—

TABLE 7. RELATIVE ACTIVITIES OF *l*-THYROXINE AND THYROID PREPARATIONS BY DIFFERENT ROUTES OF ADMINISTRATION IN RATS

Preparation	Route	*Antigoitrogenic assay*				*Calorigenic assay*			
		Endpoint (μg./rat/day)		Relative potency on basis of:		Endpoint μg./100 Gm./day		Relative potency on basis of:	
		Total I	Thyrox. I	Total I	Thyrox. I	Total I	Thyrox. I	Total I	Thyrox. I
l-Thyroxine	S.C.	1.92*	1.92†	100	100	6.9*	6.9	100	100
Soluble thyroglobulin	S.C.	2.02*	0.55	95	349	7.2*	2.0	96	345
Thyroglobulin, Product A	P.O.	2.52*	0.74	76	259	31.8	9.28	22	74
Des. thyroid, USP, Product B	P.O.	2.73*	0.84	70	229	25.0*	7.71	28	89
Des. thyroid, Product C	P.O.	2.82*	0.78	68	246	—	—	—	—
Soluble thyroglobulin	P.O.	3.82	1.05	50	183	28.4	7.8	24	88
l-Thyroxine	P.O.	5.67	5.67	34	34	26.2	26.2	26	26

* Endpoints for total iodine were obtained by extrapolation of curve. All other values were derived from the equations of curves fitted to three or more points by method of least-squares.

† Thyroxine iodine endpoints were obtained for each preparation by multiplying the observed total-iodine endpoint by the analyzed thyroxine-iodine ratio of the preparation.

methods for determining total organic and "thyroxine" iodine. One criterion for judging two very different bioassay methods is the extent of agreement in results obtained. The antigoitrogenic and calorigenic methods were in good agreement on the activities of *l*-thyroxine and soluble thyroglobulin administered subcutaneously and orally. Disagreement was primarily limited to the assays of the denatured thyroid products. Although these preparations were equally active *within* each bioassay method, their relative activity was approximately three times greater by the goiter-prevention method. Since this method involves dosing over a two-week period versus three days for the BMR assay, it may be a better measure of the biologic activity of orally administered suspensions. That a longer treatment period may be required is indicated by the observations of Reineke, Mixner and Turner (21), who found that metabolic tests conducted throughout the antigoitrogenic assay period gave directly comparable results.

The endpoints in terms of total iodine observed in our antigoitrogenic assays are similar, on a body-weight basis, to those found by other investigators (17, 22). The relation of oral to parenteral activity is identical with that reported by Frieden *et al.* (6) for three out of four thyroid products administered as suspensions. However, Thompson *et al.* (23) found that desiccated thyroid given orally was only 62 per cent as active as thyroxine given intravenously. The results of our oral comparisons indicate that denatured thyroglobulin is at least as active and possibly more active than the undenatured protein.

The accuracy of "thyroxine" iodine determinations of thyroid materials

may be questioned. By the Blau (20) method the various thyroid preparations used in these experiments ranged from 27.4 to 30.9 in ratio of "thyroxine" iodine to total iodine. Roche and Michel (24), using a different method of analysis, reported ratios of 30–34 per cent for normal mammalian thyroids of many species.

Our control analyses with *dl*- and *l*-thyroxine gave 88–90 per cent of the theoretical iodine. Our analyses for "thyroxine" iodine may be 10–12 per cent too low. Correction of the relative potencies (Table 7) by that amount does not significantly alter the pattern of the estimates.

Our report (13) that parenterally administered crystalline thyroxine (Squibb) and thyroglobulin are equal in calorigenic activity on a total iodine basis assumed that the thyroxine was completely racemized during its isolation by alkaline hydrolysis. According to recent information (25) the amount of racemization is small, the specific rotation being about −4°. Therefore, this thyroxine is largely in the *l* or levo form.

How may the marked quantitative superiority of thyroglobulin over *l*-thyroxine in terms of *l*-thyroxine content be explained? One possibility is that thyroglobulin or products of its proteolysis are more slowly absorbed parenterally and orally, more slowly metabolized, and thus more effective. The observation that intravenously administered thyroglobulin is equally effective calorigenically within the same period of time as after subcutaneous and oral administration suggests that rate of absorption is not a primary factor. Another possibility is that thyroid may contain enough *l*-triiodothyronine, reported to be three to seven times more active than *l*-thyroxine in assays on laboratory animals (26, 27), to account for the difference. This possibility appeared likely when it was found that 84 per cent of the iodine in *l*-triiodothyronine is recoverable by the Blau method as apparent "thyroxine" iodine (28), as suggested by Tomich and Woollett (27). However, no quantitative method for determining triiodothyronine in thyroid has been developed. Qualitative reports suggest that the amount normally present is too small (29) to account for the differences observed between the activities of *l*-thyroxine and thyroglobulin.

It should be noted that we have converted all biologic and chemical data to a total iodine or "thyroxine" iodine basis, to permit quantitative comparison. The three commercial products, however, were distinctly different in total iodine and "thyroxine" iodine content, as shown in Table 1. Qualitative differences in biologic activity between *l*-thyroxine, purified thyroglobulin and whole thyroid have not been investigated in this study.

SUMMARY

1. Two methods of bioassay have been used to determine the activities of *l*-thyroxine sodium pentahydrate and an experimental soluble thyro-

globulin preparation, by different routes of administration. For comparison, three commercial products, thyroglobulin "A" and desiccated thyroid "B" and "C," were assayed as suspensions orally (p.o.).

2. The activities observed by *antigoitrogenic assay* were calculated on a relative scale by assigning the value 100 to the activity of *l*-thyroxine administered subcutaneously (s.c.). Calculations were on two bases:

a) In terms of *"thyroxine" iodine:* soluble thyroglobulin s.c. 349; Product "A" p.o. 259; Product "B" p.o. 246; Product "C" p.o. 229; soluble thyroglobulin p.o. 183; *l*-thyroxine sodium p.o. 34.

b) In terms of *total organic iodine:* soluble thyroglobulin s.c. 95; Product "A" p.o. 76; Product "B" p.o. 70; Product "C" p.o. 68; soluble thyroglobulin p.o. 50; *l*-thyroxine sodium p.o. 34.

3. Calorigenic activity ratios (calculated as under 2):

a) In terms of *"thyroxine" iodine:* soluble thyroglobulin s.c. 345; Product "B" p.o. 89; soluble thyroglobulin p.o. 88; Product "A" p.o. 74; *l*-thyroxine sodium p.o. 26.

b) In terms of *total organic iodine:* soluble thyroglobulin s.c. 96; Product "B" p.o. 28; *l*-thyroxine sodium p.o. 26; soluble thyroglobulin p.o. 24; Product "A" p.o. 22.

4. The two methods of assay were in close agreement on the relative potencies of *l*-thyroxine sodium and soluble thyroglobulin administered as solutions s.c. and p.o. The methods disagreed on the activities of the commercial products. Antigoitrogenically, they were three times more active than calorigenically. However, *within* each method the products were equally active.

5. Soluble thyroglobulin is equally active calorigenically when administered intravenously, intraperitoneally and subcutaneously.

6. These observations on over 800 rats are interpreted as:

a) demonstrating the importance of biologic assay when comparing thyroxine and other iodinated thyronines with thyroid preparations, by the same or different routes of administration;

b) further confirmation of many published reports that the activity of the natural thyroid protein, thyroglobulin, is considerably greater than can be accounted for by its chemically determined "thyroxine" iodine or "thyroxine-like" content;

c) evidence that rate of absorption does not explain the difference.

Acknowledgments

The technical assistance of the following persons who participated in the work at various times is gratefully acknowledged: Mr. George Feri, Mr. Thomas Pyrzynski, and Miss Vivian Beach; for animal care, Mrs. Francis Mackenzie and Miss Helen Murray.

REFERENCES

1. MEANS, J. H.: The Thyroid and Its Diseases, ed. 2. Philadelphia, J. B. Lippincott Company, 1948, pp. 55–64.
2. SALTER, W. T.; LERMAN, J., and MEANS, J. H.: The calorigenic action of thyroxin polypeptide, *J. Clin. Invest.* **12**: 327, 1933.
3. MEANS, J. H.; LERMAN, J., and SALTER, W. T.: The role of thyroxine iodine and total organic iodine in the calorigenic action of whole thyroid gland, *J. Clin. Invest.* **12**: 683, 1933.
4. GADDUM, J. H.: Quantitative observations on thyroxine and allied substances. II. Effects on oxygen consumption of rats, *J. Physiol.* **68**: 383, 1930.
5. FRIEDEN, E., and WINZLER, R. J.: Comparative parenteral thyroxine-like activity of natural and synthetic thyroproteins studied with the goiter prevention method, *Endocrinology* **43**: 40, 1948.
6. FRIEDEN, E.; TUCKICH, E. B., and WINZLER, R. J.: Comparative oral thyroxine-like activity of natural and synthetic thyroproteins and of DL-thyroxine studied with the goiter prevention method, *Endocrinology* **45**: 82, 1949.
7. WHITE, J.; MCGINTY, D. A.; ANDERSON, L. P., and WHITE, F. R.: The influence of desiccated thyroid, thyroid concentrate and thyroxine on the oxygen consumption of the guinea pig, *Endocrinology* **24**: 693, 1939.
8. HAMILTON, C. F.; ALBERT, A., and POWER, M. H.: Bio-assay of calorigenic substances using tadpoles of Xenopus laevis, *Endocrinology* **43**: 406, 1948.
9. PALMER, W. W., and LELAND, J. P.: Comparative calorigenic action of normal and pathological thyroid glands administered in equithyroxine doses, *J. Clin. Invest.* **14**: 619, 1935.
10. FOSTER, G. L.; PALMER, W. W., and LELAND, J. P.: A comparison of the calorigenic potencies of *l*-thyroxine, *dl*-thyroxine, and thyroid gland, *J. Biol. Chem.* **115**: 467, 1936.
11. MEYER, A. E., and WERTZ, A.: The calorigenic efficiency of thyroid material in relation to thyroxine and to iodine content, *Endocrinology* **24**: 683, 1939.
12. CORTELL, R. E.: The antithyroxine activity of thyroxine analogs, *J. Clin. Endocrinol.* **9**: 955, 1949. *Tr. Am. Goiter A.* p. 44 ,1949.
13. KROC, R. L., and STASILLI, N. R.: Calorigenic activities of thyroxine and thyroglobulin, *Fed. Proc.* **11**: 86, 1952.
14. BARKER, S. B.: Effects of thyrotrophin on metabolism of thiouracil-treated rats, *Endocrinology* **37**: 230, 1945.
15. BENEDICT, F. G.: A multiple chamber respiration apparatus for rats and other small animals, *J. Nutrition* **3**: 161, 1930.
16. KROC, R. L., and STASILLI, N. R.: Unpublished material.
17. DEMPSEY, E. W., and ASTWOOD, E. B.: Determination of the rate of thyroid hormone secretion at various environmental temperatures, *Endocrinology* **32**: 509, 1943.
18. ROBBINS, J., and RALL, J. E.: Zone electrophoresis in filter paper of serum I^{131} after radioiodide administration, *Proc. Soc. Exper. Biol. & Med.* **81**: 530, 1953.
19. BECKER, E.: Personal communication.
20. BLAU, N. F.: Determination of thyroxine iodine, *J. Biol. Chem.* **110**: 351, 1935.
21. REINEKE, E. P.; MIXNER, J. P., and TURNER, C. W.: Effect of graded doses of thyroxine on metabolism and thyroid weight of rats treated with thiouracil, *Endocrinology* **36**: 64, 1945.
22. LITTRELL, J. L.; KELSEY, C.; DOLGIN, A., and FEVOLD, H. L.: Comparative activities

of thyroxine and its monosodium and disodium salts, *Proc. Soc. Exper. Biol. & Med.* **81**: 670, 1952.

23. Thompson, W. O.; Thompson, P. K.; Taylor, S. G.; Nadler, S. B., and Dickie, L. F. N.: The pharmacology of the thyroid in man, *J.A.M.A.* **104**: 972, 1935.
24. Roche, J., and Michel, R.: Natural and artificial iodoproteins, *in* Advances in Protein Chemistry, edited by Anson, Edsall and Bailey. New York, Academic Press Inc., 1951, vol. 6, p. 253.
25. Borman, A. Personal communication.
26. Gross, J., and Pitt-Rivers, R.: 3:5:3′-Tri-iodothyronine. 2. Physiological activity, *Biochem. J.* **53**: 652, 1953.
27. Tomich, E. G., and Woollett, E. A.; The biological activity of triiodothyronine, *Lancet* **1**: 726, 1953.
28. Phillips, G. E.: Unpublished material.
29. Gross, J., and Pitt-Rivers, R.: 3:5:3′-Triiodothyronine. 1. Isolation from thyroid gland and synthesis, *Biochem. J.* **53**: 645, 1953.
30. Abramowitz, A. A.; Money, W. L.; Zarrow, M. X.; Talmage, R. V. N.; Kleinholz, L. H., and Hisaw, F. L. Preparation, biological assay and properties of relaxin, *Endocrinology* **34**: 103, 1944.
31. Frieden, E. H., and Hisaw, F. L.: Purification and properties of relaxin, *Arch. Biochem.* **29**: 166, 1950.

PRELIMINARY EXPERIENCE IN THE TREATMENT OF HYPERTHYROIDISM WITH POTASSIUM PERCHLORATE*†

ANN F. GODLEY, M.D. AND JOHN B. STANBURY, M.D.

The Departments of Medicine of the Harvard Medical School and of the Massachusetts General Hospital, Boston, Massachusetts

THE observations by MacKenzie (1) and Astwood (2, 3) and their associates of the striking effects of thiourea and related substances upon the thyroid gland have revolutionized the clinical management of patients with thyrotoxicosis. These drugs exert their favorable effect by preventing the incorporation of iodide into molecular combination with tyrosyl groups within the thyroid gland, but they do not prevent the trapping of iodide from the blood by the parenchymal cells of the gland (4). At the present time propylthiouracil, methylthiouracil and 1-methyl-2-mercaptoimidazole (methimazole) are widely employed in the preparation of thyrotoxic patients for surgery, and to a lesser extent in the chronic control of the overactive thyroid gland (5).

Certain simple anionic substances also possess antithyroid activity. Barker (6) in 1936 observed that in patients who receive intensive thiocyanate therapy for hypertension an enlargement of the thyroid gland may develop, which can be reversibly inhibited by adding iodide to the diet. It has been shown that thiocyanate prevents the trapping of iodide by the gland (7). Attempts at using thiocyanate in the treatment of Graves' disease have not been successful, presumably because its antithyroid activity is easily inhibited by small amounts of iodide.

In an investigation of other anionic substances for antithyroid activity in the rat, Wyngaarden, Wright and Ways (8) found that oral or parenteral administration of nitrate or perchlorate inhibits the uptake of iodide by the gland, and causes a release of trapped iodide from the gland. If either sub-

Received for publication July 30, 1953.

* Presented at the Annual Meeting of the American Goiter Association, Chicago, Ill., May 7–9, 1953.

This article will be included in the bound volume of the 1953 "Transactions of the American Goiter Association" published by Charles C Thomas, Publisher, which will be available for purchase early in 1954.

† Supported by the Atomic Energy Commission under contract AT(30–1)667, and by a grant from Parke-Davis and Co., Detroit, Michigan.

stance is given continuously in the diet, intense hyperplasia of the thyroid gland results. When compared with iodide, nitrate and thiocyanate, perchlorate is the most potent in preventing the uptake of a tracer dose of radioactive iodine (9).

Perchlorate prevents accumulation of iodide in the thyroid gland of the patient with Graves' disease (10). When perchlorate is given prior to administration of radioiodine, the isotope fails to appear in appreciable concentration in the gland. When radioactive iodide is allowed to accumulate in the thyroid of the methimazole-treated patient, the labeled iodide can be quantitatively discharged from the gland by administering potassium perchlorate.

The effectiveness of perchlorate in preventing access of iodide to the thyroid suggested a therapeutic trial in patients with Graves' disease. This report is a survey of the results which have been obtained in the first 24 patients.

METHODS

The diagnosis of Graves' disease was suspected in each patient because of the classic symptoms and clinical findings characteristic of that disease. Patients with equivocal signs or symptoms and those with nodular goiter were not accepted for this series. The diagnosis in each case, with one exception, was confirmed by demonstrating at least two of the following: a distinct elevation in basal metabolic rate, a high serum concentration of protein-bound iodine, and an increased 48-hour retention of radioactive iodine. In most cases all three tests were made. The dosage of potassium perchlorate was usually 200 milligrams every eight hours, but it was varied slightly for a few patients. The patients were seen at frequent intervals throughout the course of therapy. During the early weeks of treatment the first 8 patients had weekly determinations of the thyroidal uptake of radioiodine, serum concentration of protein-bound iodine and basal metabolic rate, as well as examination of blood and urine. Later these were made at biweekly intervals. Laboratory examinations were performed less frequently on subsequent patients.

When the euthyroid state was achieved, some of the patients underwent subtotal thyroidectomy, some were given iodide in addition to the perchlorate in preparation for surgery, and some received the perchlorate on a continuing basis.

RESULTS

The patients are classified in Table 1 according to plan of treatment. Fourteen patients were prepared for surgery and underwent a subtotal thyroidectomy. Five of these were given saturated solution of potassium iodide for a few days immediately before surgery in order to obtain the

TABLE 1. DISTRIBUTION OF PATIENTS TREATED WITH POTASSIUM PERCHLORATE

Prepared for thyroidectomy		14
Pre-treated with potassium iodide	5	
No pre-treatment with potassium iodide	8	
Escape from iodide control; subsequent preparation with methimazole	1	
Continuously treated—euthyroid		5
Treatment now discontinued	2	
Became euthyroid but escaped from control during potassium iodide therapy		2
Became euthyroid—lost to follow-up		1
Discontinued—? toxic reactions		2
	Total	*24*

involuting effect of iodide on the hyperplastic gland. In retrospect, 1 and possibly 2 of these patients had begun to escape from complete control after iodide therapy was started. In one of them, a rise in blood pressure and pulse during the surgical procedure necessitated limitation of the operation to a hemithyroidectomy. The opposite lobe was removed uneventfully at a later date, perchlorate being given in the interval. Another of these patients, whose preparation for surgery was marked by a severe attack of recurrent pyelonephritis and who had an uneventful surgical thyroidectomy, was two months pregnant at the time of operation. She had had one child previously but had been unable to conceive for seven years until she became euthyroid during perchlorate therapy. A sixth patient experienced a severe recrudescence of symptoms and signs of thyrotoxicosis after receiving 10 drops daily of a saturated solution of potassium iodide; his scheduled surgery was therefore cancelled. He had been hypothyroid, with a basal metabolic rate of −16 per cent, immediately before the iodide was begun. He was prepared subsequently with methimazole and had an uneventful thyroidectomy.

Eight patients underwent subtotal thyroidectomy without preoperative potassium iodide. There appeared to be little difference in the vascularity of the glands of those patients who received potassium iodide as compared with those who did not, although 1 patient of the latter group had an exceedingly vascular gland which created a difficult problem in hematosis. One of these patients had a rise in pulse rate to 150 during the operative procedure after half the gland had been removed. Subtotal thyroidectomy was completed at a later date. Perchlorate was given during the intervening time.

Five patients with Graves' disease received perchlorate on a continuous

basis and are now euthyroid. Two of these discontinued the drug without recurrence of the disease. Two other patients became euthyroid while taking perchlorate, but when potassium iodide was given in preparation for surgery each experienced a rapid return of the signs and symptoms of thyrotoxicosis. Both are responding again to perchlorate alone. One patient has been lost to follow-up. In 2 of the 24 patients complications developed which necessitated withdrawal of the drug.

Response of the serum protein-bound iodine: The concentration of protein-bound iodine was measured frequently in the serum of the first 8 patients. As may be seen from Figure 1, the modal time of response was four weeks, but there was wide variation in the response rate. The fall in concentration of the blood hormonal iodine appeared to be more rapid than the clinical response or the fall in basal metabolic rate. Later patients showed a fall in serum protein-bound iodine concentration to normal, but usually only initial and final blood determinations were obtained.

Response of the basal metabolic rate: The approach of the basal metabolic rate toward normal is shown in Figure 2 for 20 of the 24 patients. The

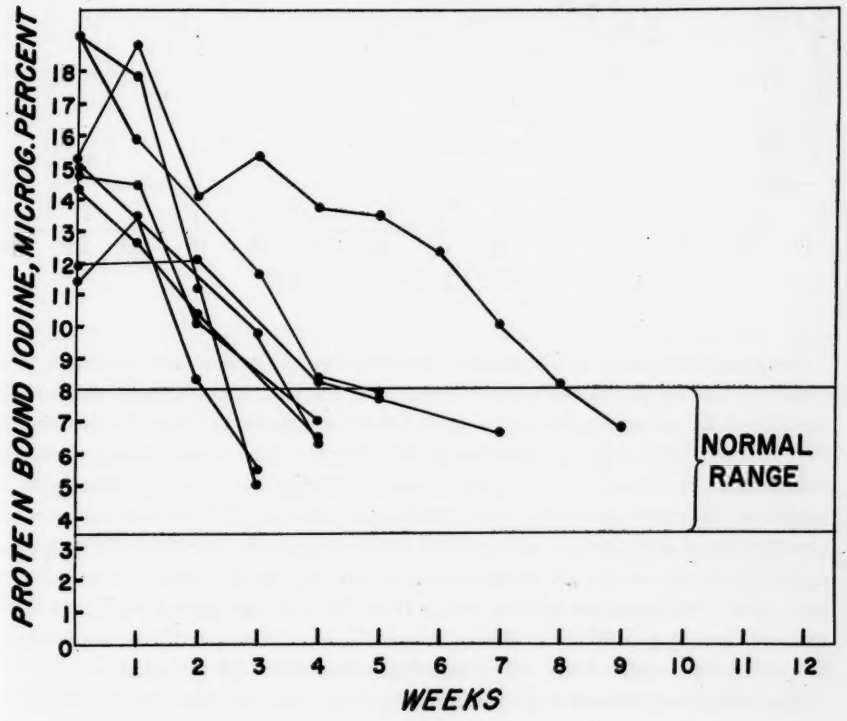


FIGURE 1

modal time required to reach a normal or nearly normal basal metabolic rate was from four to eight weeks, but again there was considerable variation in the response rate. A few patients responded very slowly in spite of an excellent block to accumulation of iodide in the gland.

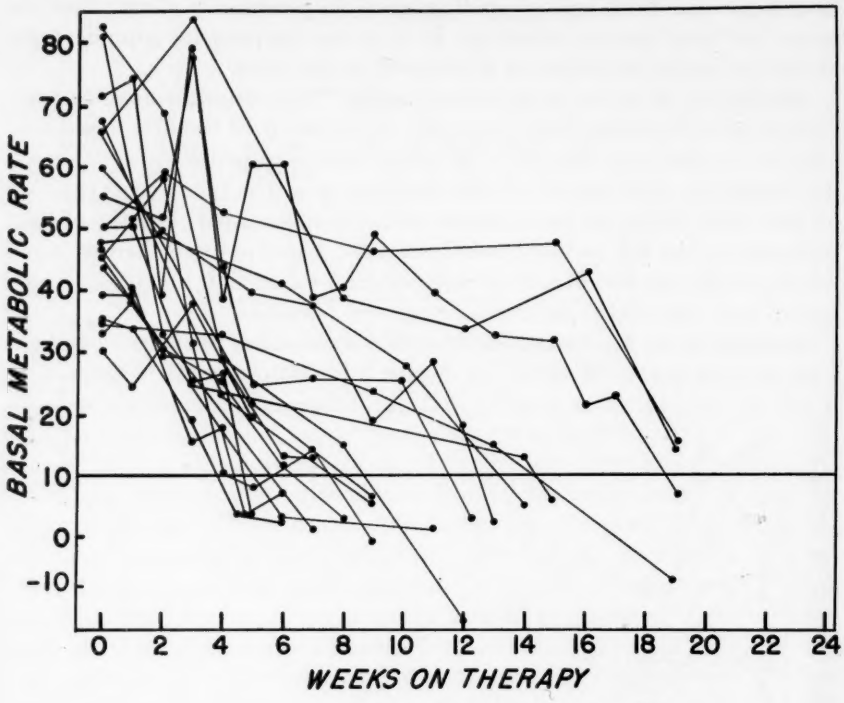


FIGURE 2

Radioactive iodine uptake by the thyroid: This test was performed on all patients before perchlorate was begun. In all but 1 the initial thyroidal uptake determination at forty-eight hours was greater than 60 per cent. One patient who had an uptake of 18 per cent had been taking Lugol's solution until a few days before beginning perchlorate therapy. Her clinical response to perchlorate was slow. Thirteen patients had determinations of the uptake of radioactive iodine both before beginning perchlorate therapy and within two weeks after medication was begun. The mean control uptake was 77.5 per cent, with a range from 60.7 to 108 per cent. The mean uptake during perchlorate therapy was 15.9 per cent, with a range from 3.4 to 38.8 per cent. Only three uptakes were above 20 per cent.

Continuous treatment with perchlorate: Five patients were given perchlorate in order to assess the effects of continuous medication. All 5 became

euthyroid after a few weeks of treatment and have remained so. The result obtained in these patients is shown in Figure 3. When the drug was discontinued after twenty-eight weeks there was an immediate return of the thyrotoxicosis. Therapy was resumed. The drug was again discontinued after fifty-two weeks but the disease has not returned, although there is still enlargement of the thyroid gland. One patient discontinued medication

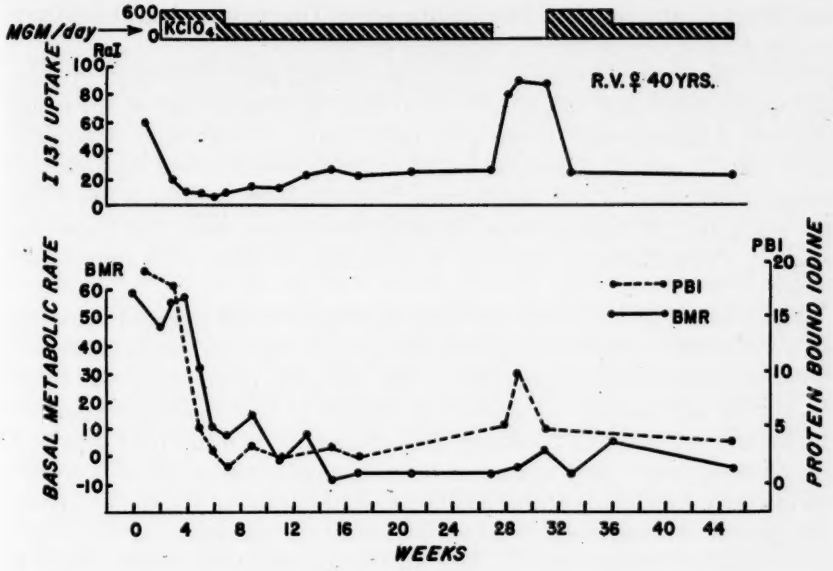


FIGURE 3

after eleven weeks. She failed to keep her appointments and, when seen twelve weeks later, was euthyroid by clinical and by laboratory examination. She has remained so for the intervening five months. It has been possible to reduce the dosage in 2 patients. One is the subject of Figure 3. The other is maintained in the euthyroid state on a single daily dose of 100 milligrams.

Surgical aspects: It was the consensus of the operating surgeons, most of whom were members of the resident staff, that a few of these glands were more vascular than glands of patients prepared in the conventional way with propylthiouracil and iodide. One of the most recent patients to undergo subtotal thyroidectomy seemed to be particularly well prepared by the addition of a single drop of a saturated solution of potassium iodide to the daily perchlorate regimen for a week prior to surgery, but during the same dosage in another patient there was escape from control and a recrudes-

cence of thyrotoxicosis. The problem may be that of achieving the proper balance between the perchlorate and the iodide medication, in order that full advantage may be taken of the blocking effect of perchlorate and the involuting effect of iodide.

There was only one important operative complication. Two patients accumulated fluid in the wound, to a degree sufficient to cause stridor; one required temporary tracheotomy. Two patients had minimal and temporary tetany immediately following operation. One patient had temporary partial paresis of a recurrent laryngeal nerve.

Toxic effects: Perchlorate was withdrawn from 2 patients because of signs and symptoms which might have been toxic manifestations of the drug. One was a 57-year-old woman with mild Graves' disease and congestive heart failure, who had complained of upper gastrointestinal distress and nausea before perchlorate was begun. The symptoms became worse when she was given 200 milligrams of the drug three times daily, but improved when it was withdrawn. She was subsequently treated with radioactive iodine.

The second toxic reaction was more impressive. A 22-year-old secretary with moderately severe Graves' disease of long standing had become severely anorectic a month previous to her first visit to the hospital. A few days after perchlorate was started she began to have burning epigastric discomfort and frequent vomiting. This culminated in a ruptured duodenal ulcer a week later. She was treated without surgery and made an uneventful recovery from the perforation. X-ray examination of the upper gastrointestinal tract disclosed a scarred duodenal cap. She was able to tolerate methimazole without distress, had an uneventful thyroidectomy and is free of symptoms at the present time, but is on a strict medical regimen for her ulcer.

There have been no other toxic manifestations. There were no significant changes in the formed elements of the blood. Two patients were observed to have minimal albuminuria in tests on occasional specimens, whereas there had been no albuminuria before perchlorate was begun. Two patients showed pyuria on occasional tests, while taking perchlorate; one of these had a long history of pyelonephritis. There was no evidence of liver damage, and the only skin rash which was noted disappeared when phenobarbital was withdrawn.

Particular indications: One patient served particularly well to illustrate an especial area of usefulness for potassium perchlorate. A 47-year-old housewife with symptoms of thyrotoxicosis for the previous two years was given methimazole therapeutically four months before entering the hospital. Two weeks later a punctate and urticarial rash and severe arthralgia developed, requiring withdrawal of the drug. She was then given propylthiouracil, but the rash promptly reappeared. Lugol's solution was then

begun and continued for the next nine weeks. Although she gained a little weight her symptoms of thyrotoxicosis increased. At the time of admission to the hospital her basal metabolic rate was +35 per cent. The signs and symptoms were those of moderately severe Graves' disease. Her therapeutic response to potassium perchlorate was slow, but when she reached the euthyroid state a subtotal thyroidectomy was performed without incident.

DISCUSSION

Potassium perchlorate appears to be an effective agent for controlling the hyperthyroidism of patients with Graves' disease. The symptoms of the disease are mitigated and there is a return to normal of the elevated basal metabolic rate and serum concentration of hormonal iodine. The mode of action of this substance is to deny access of iodide to the thyroid gland.

The rate at which the patient responds to therapy has been found to vary widely, but in general compares favorably with the response rates to antithyroid drugs of the thiourea series (11). No patient has failed to respond in time, but several responded slowly. One of these was receiving large doses of iodine just before perchlorate was begun. Presumably the thyroid of this patient was filled with iodine, which had to be exhausted before a therapeutic effect could be achieved. The other patients who responded slowly had unusually large goiters which were probably filled with stored hormone.

From the surgical point of view the preparation of the gland for excision has left something to be desired. When saturated solution of potassium iodide was given, the thyrotoxicosis of a few of the patients escaped from adequate control. It was long ago shown that a few milligrams of potassium iodide is adequate to involute the thyroid gland of Graves' disease (12). The use of larger doses of perchlorate and smaller doses of iodide may answer the problem of vascularity and escape from control.

The only toxic symptoms which were encountered arose from irritation of the gastrointestinal tract. Although it was by no means certain that perchlorate was responsible for these symptoms or for the duodenal perforation of one of the patients, it must be assumed that this was the case, until further experience has accumulated. Other patients received two to three times the daily dosage of the 2 patients who had gastrointestinal symptoms; yet they did not experience abdominal distress. It remains to be seen whether wider experience with perchlorate will disclose toxic reactions which have not appeared in the present limited series.

SUMMARY

Potassium perchlorate has been used in the treatment of 24 patients with Graves' disease. Oral administration of 200 to 400 milligrams every

eight hours was effective in controlling the disease, as demonstrated by symptomatic improvement of the patient and a return to normal of the basal metabolic rate and serum concentration of protein-bound iodine.

Thirteen patients had subsequent subtotal thyroidectomies. Two patients are euthyroid and have stopped treatment, and the remainder are either being treated continuously or have had their treatment interrupted. Preoperative addition of potassium iodide to the perchlorate caused an escape from control of the thyrotoxicosis in several patients. Two reactions which possibly were toxic manifestations of potassium perchlorate involved the gastrointestinal tract.

Potassium perchlorate is an effective antithyroid agent in the preoperative or continuous treatment of thyrotoxicosis. It is of particular value in those patients who are sensitive to, or fail to respond to the drugs of the thiourea group or iodide. Further experience and study are required for full evaluation of this new antithyroid drug.

REFERENCES

1. MacKenzie, J. B.; MacKenzie, C. C., and McCollum, E. V.: The effect of sulfanilylguanidine on the thyroid of the rat, *Science* **94**: 518–519, 1941.
2. Astwood, E. B.; Sullivan, J.; Bissell, A., and Tyslowitz, R.: Action of certain sulfonamides and of thiourea upon the function of the thyroid gland of the rat, *Endocrinology* **32**: 210–225, 1943.
3. Stanley, M. M., and Astwood, E. B.: Determination of the relative activities of antithyroid compounds in man using radioactive iodine, *Endocrinology* **41**: 66–84, 1947.
4. Astwood, E. B.: Mechanisms of action of various antithyroid compounds, *Ann. New York Acad. Sci.* **50**: 419–443, 1949.
5. Irwin, G. W.; VanVactor, H. D., and Norris, M. S.: Propylthiouracil and methimazole therapy—comparative experiences, *J. A. M. A.* **148**: 45–47, 1952.
6. Barker, M. N.: The blood cyanates in the treatment of hypertension, *J. A. M. A.* **106**: 762–767, 1936.
7. VanderLaan, J. E., and VanderLaan, W. P.: The iodide concentrating mechanism of the rat thyroid and its inhibition by thiocyanate, *Endocrinology* **40**: 403–416, 1947.
8. Wyngaarden, J. B.; Wright, B. M., and Ways, P.: The effect of certain anions upon the accumulation and retention of iodide by the thyroid gland, *Endocrinology* **50**: 537–549, 1952.
9. Wyngaarden, J. B.; Stanbury, J. B., and Rapp, B.: The effects of iodide, perchlorate, thiocyanate, and nitrate administration upon the iodide concentrating mechanism of the rat thyroid, *Endocrinology* 52: 568–574, 1953.
10. Stanbury, J. B., and Wyngaarden, J. B.: Effect of perchlorate on the human thyroid gland, *Metabolism* **1**: 533–539, 1952.
11. Bartels, E. C., and Sjogren, R. W.: 1-Methyl-2-mercaptoimidazole: a new active antithyroid agent, *J. Clin. Endocrinol. & Metab.* **11**: 1057–1062, 1951.
12. Thompson, W. O.; Brailey, A. G., and Thompson, P. K.: The effective range of iodine dosage in exophthalmic goiter. Preliminary report, *J. A. M. A.* **91**: 1719, 1928.

STRUMA LYMPHOMATOSA: CLINICAL MANIFESTATIONS AND RESPONSE TO THERAPY*

WALTER E. FURR, JR., M.D. AND GEORGE CRILE, JR., M.D.

The Department of General Surgery, Cleveland Clinic, and the Frank E. Bunts Educational Institute, Cleveland, Ohio

STRUMA lymphomatosa is generally considered to be a clinicopathologic entity, of which the cause remains unknown. In recent years some have considered it to be a degenerative disease, in contrast to the earlier views that it was of inflammatory origin (1, 2, 3). Until recently, a correct diagnosis was not often made preoperatively. The treatment remains in dispute.

This study summarizes the clinical features of 62 cases of struma lymphomatosa studied at the Cleveland Clinic from January 1940 through December 1952, in which the diagnosis was established by thyroidectomy or needle biopsy.

Dr. J. B. Hazard of the Department of Surgical Pathology reviewed the histologic material of all the cases and roughly graded each specimen as to the degree of lymphocyte infiltration, fibrosis and lymph node formation.

CLINICAL DATA

Of the 62 cases of struma lymphomatosa the majority were in women—90.4 per cent.

The symptoms were varied but were related to the goiter either directly or indirectly. The chief complaint of 42 patients was the presence of a goiter. Sixteen complained primarily of a pressure sensation in the neck, or of anxiety. Pressure, hoarseness, choking, goiter and slight tenderness accounted for the majority of the secondary complaints. Nervousness and fatigue were present in 20 per cent.

Examination of the thyroid revealed bilateral enlargement in 39 cases (62 per cent). The gland was considered nodular in 37 cases (59 per cent). The consistency of the gland varied. It was considered hard or unusually firm to palpation in 77 per cent of the cases.

Received for publication May 9, 1953.

* Presented at the Annual Meeting of the American Goiter Association, Chicago, Ill., May 7–9, 1953.

This article will be included in the bound volume of the 1953 "Transactions of the American Goiter Association," published by Charles C Thomas, Publisher, which will be available for purchase early in 1954.

In approximately half of the patients the diagnosis was thyroiditis, before operation. A preoperative diagnosis of struma lymphomatosa was made in 19 cases (30.6 per cent) as a result of the history and physical findings. In another 11 cases (18 per cent) the diagnosis was merely chronic thyroiditis. Twenty-five patients (40.3 per cent) were considered to have a nodular goiter. This was the most frequent error in diagnosis.

Routine laboratory examinations revealed no significant abnormality. An anemia was occasionally noted and leukocyte counts tended to be slightly lower than the average. A leukocyte count less than 6,000 per cu. mm. was present in 43 per cent of the cases. The erythrocyte sedimentation rate was elevated (.75–1.55 mm./min.) in 8 of 10 cases studied. Achlorhydria was present in 5 of 9 cases studied.

The basal metabolic rate was zero or below in 39 of 49 cases studied. Clinical myxedema was present in 6 cases (9.6 per cent). There was usually a normal radioactive iodine uptake by the thyroid (Table 1).

TABLE 1. THYROIDAL RADIOACTIVE IODINE UPTAKE (24-HOUR) IN 17 CASES STUDIED

Uptake, %	No. of cases
0–15	5
16–30	9
31–60	3
Basal metabolic rate in 49 cases studied	
BMR, %	No. of cases
+11 to +30	2 } 10
0 to +10	8 }
0 to −10	14 }
−11 to −20	16 }
−21 to −30	5 } 39
−31 to −40	3 }
−41 to −50	1 }

A laryngeal examination was performed in 7 patients who had hoarseness. Five of these patients had a pathologic condition of the vocal cord. One patient had paresis of the right vocal cord as a result of previous surgery. Chronic laryngitis, hyperkeratosis of the vocal cord, papilloma and a myxomatous polyp were discovered in the other patients.

There was little indication from these cases that pregnancy was a precipitating factor in the development of struma lymphomatosa. Only 4

patients gave a history of having first noted their goiters in the postpartum period, three to five months after delivery.

Tabulation revealed that only one third of the patients with struma lymphomatosa did not have an associated disease (Table 2). Cardiovascular

TABLE 2. DISEASES ASSOCIATED WITH STRUMA LYMPHOMATOSA

Diseases		No. of cases
Cardiovascular disease		11
Hypertension	6	
Arteriosclerotic heart disease	4	
Coronary heart disease	1	
Anxiety state		13
Obesity (marked)		7
Arthritis		6
Diabetes mellitus		2
Vocal cord pathology		5
No associated disease		22
Addison's disease (developed 2 years after diagnosis of struma lymphomatosa)		1

disease was present in 11 cases (17 per cent). Hypertension is mentioned frequently in cases reported in the literature; it occurred in only 6 patients of this series. An anxiety state was diagnosed in 13 patients; possibly it was another manifestation of the disease or it might have been coincidence. This absence of well-being may or may not respond to the various forms of therapy. In the few patients treated with cortisone, all remarked about the disappearance of this feeling after the first few doses. Myxedema was present in 6 cases (9.6 per cent). Five of these patients had hoarseness.

An attempt was made to correlate roughly the histopathology of the goiter with its increase in size and its duration (Tables 3 and 4). It was noted that marked lymphocytic infiltration was more frequent in goiters showing a recent increase in size and those present for two years or less. Fibrosis did not appear to be related to the duration of the goiter. Lymph nodule formation was seen more frequently in goiters showing a recent increase in size, but was unrelated to the duration of the goiter.

RESPONSE TO TREATMENT

The results of treatment reported here include only those in patients in whom the diagnosis was established by needle biopsy. It was believed that

TABLE 3. RELATIONSHIP OF INCREASE IN GOITER SIZE TO HISTOPATHOLOGY

Histologic feature	Degree	Increase in size of goiter (33 cases)	No increase in size of goiter (29 cases)
		No. of cases	No. of cases
Lymphocytic infiltration	0–2 plus	8	14
	3–4 plus	17	5
Fibrosis	0–2 plus	17	10
	3–4 plus	8	9
Lymph nodule formation	0–2 plus	22	17
	3–4 plus	3	2
Not graded		8	10

these particular patients furnished the basis for a more accurate appraisal of the treatment employed. X-ray therapy, desiccated thyroid, cortisone, or combinations of these were employed in the treatment (Tables 5, 6 and 7).

X-ray therapy was given in 11 cases in doses ranging from 450 to 2400 *r*. Desiccated thyroid therapy was added in 6 of these cases. Occasionally the response to x-ray therapy was rapid, a decrease in size being noted in a few days. Usually a progressive diminution in size continued; the goiter was reduced approximately 50 per cent in size in one to two months.

Desiccated thyroid (2 to 3 grains daily) was the only medication given

TABLE 4. RELATIONSHIP OF DURATION OF THE GOITER TO HISTOPATHOLOGY

Histologic feature	Degree	Goiter present 2 yrs. or less (27 cases)	Goiter present more than 2 yrs. (23 cases)
		No. of cases	No. of cases
Lymphocytic infiltration	0–2 plus	8	7
	3–4 plus	14	8
Fibrosis	0–2 plus	17	9
	3–4 plus	5	6
Lymph nodule formation	0–2 plus	17	10
	3–4 plus	5	5
Not graded		5	8

TABLE 5. RESULTS OF X-RAY THERAPY (AFTER NEEDLE BIOPSY)

Case No.	Dose of x-ray (*r*)	Dose of des. thyroid (grs.)	Immediate response of thyroid gland (1–6 mo.)	Recurrence of disease	Well	Follow-up
3	1,800	1	6 mo. Thyroid same	No	No	3 yrs. Thyroid normal
13	2,000	1	9 days. Gland decreased ⅓	No	Yes	4 yrs. Goiter gone
14	450	—	Felt better after 1st dose	No	No	2 yrs. Thyroid still enlarged
15	1,500	—	2 mo. Gland same. 7 mo. Thyroid not palpable	No	No	5 yrs. Thyroid not palpable
16	1,550	2	1 mo. Thyroid barely palpable	No	No	4 yrs. Thyroid not palpable
28	600	—	1 mo. Slight dec. in size	Poor response		2 mo. Thyroid hard; lobectomy
29	1,950	2	4 mo. Goiter gone	—	No	3 yrs. Thyroid not palpable
31	2,050	—	1 mo. Thyroid same	—	—	No follow-up
39	1,800	3	2 mo. Thyroid smaller	No	—	2 yrs. Thyroid not palpable
47	1,200	1	1 mo. Gland 50% smaller	No	Yes	7 mo. Thyroid sl. enlarged
55	2,400	2	1 mo. Gland 20% smaller	No	Yes	1 yr. Thyroid not palpable

in 12 cases. Decrease in size of the goiter was noted in 1 case in less than one month. In most cases the size of the gland decreased 50 per cent in from four to six months. Three patients received a daily dose of less than 2 grains; 2 of these patients still had a goiter after 1 year and 2.3 years, respectively. Desiccated thyroid was discontinued in the other case after a favorable initial response, and the goiter enlarged again within two months.

Cortisone, 100 mg. daily for five days, was given in 4 cases. A decrease in size in one week was noted in 1 case. In all 4 cases the gland decreased in size within one to two months. Desiccated thyroid (3 grains daily) was combined with the cortisone in 3 cases. In the 1 case treated with cortisone alone, the thyroid gland was normal in six months. This patient received 100 mg. of cortisone daily for six days, then 50 mg. for five days.

DISCUSSION

It has been suggested by several authors that struma lymphomatosa may be present for years without change. To substantiate this view, re-

TABLE 6. RESULTS OF DESICCATED THYROID THERAPY (AFTER NEEDLE BIOPSY)

Case No.	Dose (grs.)	Immediate response of thyroid gland (1–6 mo.)	Recurrence of disease	Well	Follow-up
1	2	5 mo. Thyroid 20% smaller	No	Yes	8 mo. Thyroid soft
23	3	6 mo. Thyroid unchanged	No	No	1 yr. Thyroid same as at 6 mo.
24	2	1 mo. Thyroid barely palpable	No	Yes	4 yrs. Thyroid not palpable
32	1	5 mo. Thyroid 30% smaller	No	Yes	2.3 yrs. Thyroid same as at 5 mo.
38	1	4 mo. Thyroid 40% smaller (des. thyroid discont'd)	Yes	No	6 mo. Goiter returned after des. thyroid stopped
42	1½	2 mo. Thyroid 60% smaller	No	No	1 mo. Thyroid smaller
43	3	5 mo. Thyroid 50% smaller	No	Yes	15 mo. Thyroid 35 Gm., soft
44	2	5 mo. Thyroid not palpable	No	Yes	18 mo. Thyroid not palpable
46	3	4 mo. Thyroid 60% smaller; soft	No	Yes	1 yr. Thyroid same as at 4 mo.
53	3	3 mo. Thyroid 50% smaller; smooth	No	Yes	1 yr. Thyroid 40 Gm.; soft
54	3	3 mo. Thyroid 25% smaller; hard	Poor response	No	5 mo. Thyroid 40 Gm.; very hard. Treated with cortisone
57	3	2 mo. Thyroid 50% smaller	No	Yes	5 mo. Thyroid not palpable

TABLE 7. RESULTS OF CORTISONE THERAPY (AFTER NEEDLE BIOPSY)

Case No.	Dose of cortisone (mg./day)	Dose of des. thyroid (grs.)	Immediate response of thyroid gland	Later response of thyroid gland
38	100×5	3	1 mo. Thyroid 50% smaller (50 Gm.)	5 mo. Thyroid 40 Gm.; soft
50	100×5	—	1 wk. Thyroid smaller	2 wks. (des. thyroid gr. 3 q.d.). Thyroid 50% smaller
			3 mo. Thyroid hard	4 mo. Thyroid unchanged
54	100×4	3	1 wk. Thyroid same	2 mo. Thyroid not enlarged; hard. Patient weak and nervous
60	100×5	—	6 days. Thyroid 50% smaller	6 mo. Thyroid normal in size and consistency

peated observations at long intervals have revealed little change in histopathology. In this study a biopsy was repeated on one thyroid gland after an interval of twenty-one years. The histopathologic picture was essentially the same. Thus the disease process persists or continues for years, with few symptoms which can be attributed to it. This study revealed that 23 patients (37.1 per cent) had a goiter for two years or more; 9 had a goiter ten years or more; and 6 for twenty years or more. The fact that the gland is not usually very large and that the disease may persist for years suggests that it may be easily overlooked.

It is possible that the rapid enlargement of a pre-existing goiter is due for the most part to lymphocytic infiltration, which is believed to compose one third to one half of the goiter. This is suggested by our data. It is shown in Tables 3 and 4 that a marked lymphocytic infiltration was more frequent in the goiters of short duration and in those goiters that had enlarged noticeably. The reason for the infiltration and its mechanism are obscure. Since the function of lymphoid tissue is poorly understood, we can only speculate on the cause of the lymphoid infiltration. It may be the result of an increase in thyroid-stimulating hormone (TSH) production by the pituitary, or a decrease in the production of potent lymphoid-moderating hormones (4).

The mechanism of action of desiccated thyroid on struma lymphomatosa can only be presumed. It is supposed that in struma lymphomatosa there is an excess of pituitary thyroid-stimulating hormone (TSH), which may be accompanied by lymphoid hyperplasia to some degree. It is possible that desiccated thyroid exerts its effect by depression of TSH production or by changes in the production of lymphoid-moderating hormones.

The action of cortisone may be similar to that of x-ray therapy, producing its effect by means of lymphocytolysis. The experimental results of the effect of hormones on lymphatic tissue show that ACTH and cortisone are the most active in producing acute involution. A short course of cortisone probably will not produce lasting results.

SUMMARY

A study of 62 cases of struma lymphomatosa is presented.

1. Recent or rapid enlargement of the thyroid is probably due to lymphocytic infiltration. The local symptoms produced may be controlled in most cases by lymphocytolytic agents such as x-rays, cortisone, or ACTH.

2. An effective treatment is the use of a maintenance dose of 2 to 3 grains of desiccated thyroid daily. Operation is not often necessary.

3. The frequency of associated pathologic conditions in the vocal cords is pointed out. It is therefore suggested that laryngeal examination be performed in all patients who have hoarseness.

REFERENCES

1. PARMLEY, C. C., and HELLWIG, C. A.: Lymphadenoid goiter; its differentiation from chronic thyroiditis, *Arch. Surg.* **53**: 190–198, 1946.
2. STATLAND, H.; WASSERMAN, M. M., and VICKERY, A. L.: Struma lymphomatosa (Hashimoto's struma); review of 51 cases with discussion of endocrinologic aspects, *A.M.A. Arch. Int. Med.* **88**: 659–678, 1951.
3. LINDSAY, S.; DAILEY, M. E.; FRIEDLANDER, J.; YEE, G., and SOLEY, M. H.: Chronic thyroiditis: a clinical and pathologic study of 354 patients, *J. Clin. Endocrinol. & Metab.* **12**: 1578–1600, 1952.
4. DOUGHERTY, T. F.: Effect of hormones on lymphatic tissues, *Physiol. Rev.* **32**: 379–401, 1952.

REVISED ANATOMY OF THE RECURRENT LARYNGEAL NERVES: SURGICAL IMPORTANCE, BASED ON THE DISSECTION OF 100 CADAVERS*

WILLIAM H. RUSTAD, M.D.

The Division of Surgery, University of California Hospital and School of Medicine, San Francisco, California

IN 1948 Brien King (1, 2) of Seattle published the results of a series of special dissections and experiments he had been conducting, which have seemed to raise the shroud of mystery and unexplained phenomena from certain phases of laryngeal behavior, especially with regard to the derangement of laryngeal function following damage to one or both recurrent laryngeal nerves. King's findings are of such importance as to make it desirable to extend his observations, since they were based on dissection experience with only 16 cadavers. We, therefore, undertook our own separate investigation of this subject at the University of California School of Medicine.

The larynx is a musculo-cartilaginous organ, the functions of which, according to Negus (3, 4), are three:

1. Protection of the respiratory tract distal to the vocal cords against the ingress of foreign particles, especially during the act of swallowing.
2. Maintenance of a patent airway.
3. Vocalization.

The functions of the larynx are carried out by four sets of muscles, to wit:

1. The adductor muscles.
2. The abductor muscle.
3. The tensor muscle.
4. The constrictor muscles.

It is elementary to state that the ability of the laryngeal muscles to carry out their several functions is dependent on their nerve supply. There is now complete agreement among those who have devoted the greatest attention to this subject that the nerve supply to the larynx is as follows:

Received for publication May 9, 1953.

* Presented at the Annual Meeting of the American Goiter Association, Chicago, Ill., May 7–9, 1953.

This article will be included in the bound volume of the 1953 "Transactions of the American Goiter Association" published by Charles C Thomas, Publisher, which will be available for purchase early in 1954.

(a) The recurrent laryngeal nerve, right and left, supplies all of the muscles of the larynx except the crico-thyroid muscle.

(b) The crico-thyroid muscle receives its innervation from the external branch of the superior larngeal nerve.

This, then, is the total motor innervation to the larynx. The internal branch of the superior layrngeal nerve supplies all of the sensation to the mucosa of the larynx, and is composed entirely of afferent fibers. It has been irrefutably demonstrated that the fibers of the internal branch of the superior laryngeal nerve do not supply motor impulses to any muscle of the larynx,

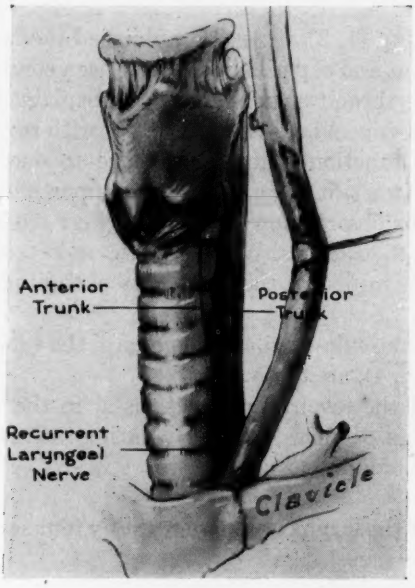


FIGURE 1

nor do they communicate or anastomose with any of its motor nerves. They do not in any degree form a nerve supply to the interarytenoideus muscles, but merely traverse the interarytenoideus in order to reach their destination, which is the mucous membrane of the larynx.

The recurrent laryngeal nerve may be considered as a single-trunk nerve when it ascends from the thorax, traverses the neck and enters the larynx without having branched at any point (with the exception of tracheal and esophageal branches). On the other hand, it may be considered as a divided nerve, when the point of division is extralaryngeal, irrespective of the point at which it divided (Fig. 1).

Our dissecting room experience[1] has revealed that the recurrent laryngeal nerve is not limited to the possibility of dividing into two branches only. We have seen one instance in which the recurrent laryngeal nerve divided extralaryngeally into six branches, all of which were clearly and unmistakably seen to enter the larynx (Fig. 2).

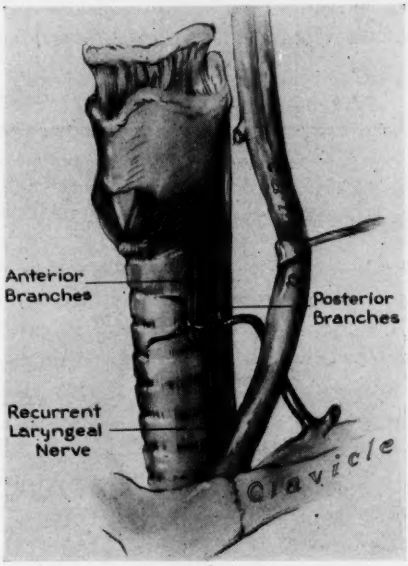


FIGURE 2

In 86 dissections we have seen 67 specimens (77.9 per cent) in which the recurrent laryngeal nerve divided into two branches; 9 specimens (10.5 per cent) in which it divided into three branches; 7 specimens (8.1 per cent) in which it divided into four branches; 2 specimens (2.3 per cent) in which it divided into five branches; and finally, 1 instance (1.2 per cent), previously mentioned, in which it divided into six terminal branches.

All of these divisions occurred extralaryngeally and all branches were seen to enter the larynx (Fig. 3) (Table 1).

Table 2 shows that of a total of 200 recurrent laryngeal nerves, 114 were single-trunk nerves, whereas 86 nerves divided at a point peripheral to the larynx. It is seen that there is no preponderance of single or divided nerves on either right or left sides.

[1] Every dissection in this series on which the conclusions are based represents the personal experience of the author in each instance.

TABLE 1. NUMBER OF DIVISIONS OF DIVIDED RECURRENT LARYNGEAL NERVES (86 NERVES)

	No. of branches				
	2	3	4	5	6
Right	40	4	6	1	
Left	27	5	1	1	1
Total	*67*	*9*	*7*	*2*	*1*
Per cent	*77.9*	*10.5*	*8.1*	*2.3*	*1.2*

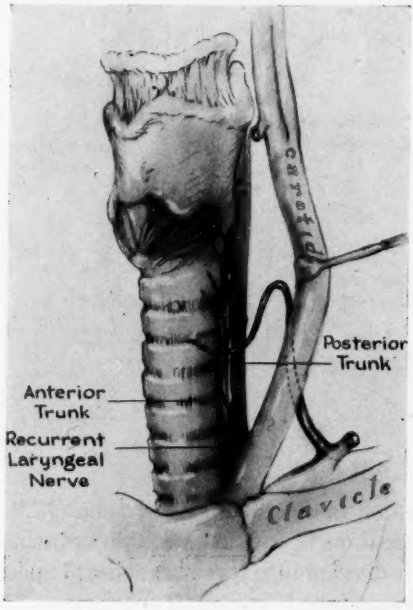


FIGURE 3

TABLE 2. DIVISION OF RECURRENT LARYNGEAL NERVE TRUNKS (200 NERVES)

Single-trunk nerves (114)			57%
Right	58	29%	
Left	56	28%	
Divided-trunk nerves (86)			43%
Right	44	22%	
Left	42	21%	

Table 3 shows that of a total of 100 cadavers 70 (35 per cent) had bilateral single-trunk nerves, and 48 (24 per cent) had bilateral divided-trunk nerves. The greater number of cadavers—82 (or 41 per cent) exhibited a single-trunk nerve on one side with a divided-trunk nerve on the other side.

In order to create a basis for specifying the level at which the recurrent laryngeal nerve divided, we chose the thyroid gland as the principal point of relationship. That area of the neck normally occupied by the isthmus

TABLE 3. TYPE OF DIVISION OF RECURRENT LARYNGEAL NERVE TRUNKS IN 100 CADAVERS

Bilateral single-trunk nerves	(70)	35%
Bilateral divided-trunk nerves	(48)	24%
Mixed single-trunk and divided-trunk nerves	(82)	41%

and main substance of the thyroid gland we have designated as the thyroid level; the area usually occupied by the superior pole, as the superior thyroid level; and the area occupied by the inferior pole and the area distal to this point, as the inferior thyroid level (Fig. 4) (Table 4).

A summation of the data shows that of the 200 recurrent laryngeal nerves, 86 or 43 per cent had divided trunks either unilaterally or bilaterally. Deleting those that divided high in the superior thyroid level (21 in number) there still remained 65 examples of divided trunks in areas frequently invaded during neck surgery. In other words, more than one third of patients can be expected to have one or more recurrent laryngeal nerve trunks dividing in the thyroid or inferior thyroid areas, and therefore these patients possess potentiality for injury of one or the other of the main trunk branches.

The recurrent laryngeal nerve, whether as a single trunk or whether broken up into a variable number of component branches, has been seen to enter into many diverse and completely unpredictable branching patterns. We may draw the analogy of a huge pipeline bringing the water supply to a community from a far-distant lake, then breaking up into several smaller conduits as the community is approached, and ultimately breaking down into many single conduits each supplying a unit of the community. In this instance, we have a community of laryngeal muscles which receives its nerve supply from a large principal conduit, the recurrent laryngeal nerve. In order that each unit of this community of muscles may receive its own nerve supply, it is clear that this one large conduit must divide and redivide to supply the individual unit. This division and subdivision often takes place intralaryngeally, but we now know that it can take place at any point peripheral to the initial branching from the vagus.

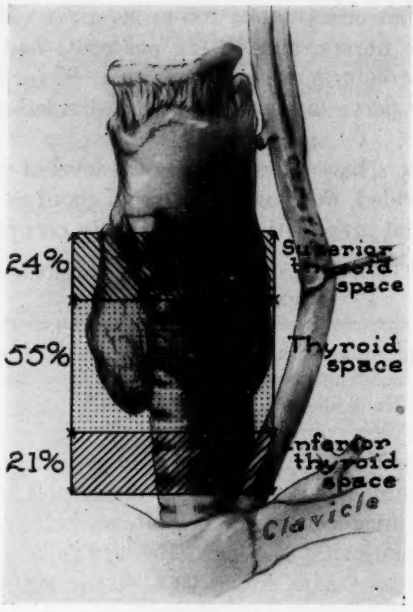


FIGURE 4

That portion of the work of Murtagh (5) devoted to the histologic studies of the intralaryngeal distribution of the recurrent laryngeal nerve has clearly shown that the nerve, intralaryngeally, invariably breaks up into four to six bundles, and frequently into as many as twelve bundles of nerve fibers. From this we may assume that it would not be too surprising to see a rare recurrent laryngeal nerve that divided extralaryngeally into twelve branches.

Fowler and Hansen (6) laid considerable stress on the vulnerable point in the neck at which the recurrent laryngeal nerve might most likely be damaged during the course of operations on the thyroid gland. These authors state that "in a large majority of cases the most intimate rela-

TABLE 4. LOCATION OF POINTS AT WHICH RECURRENT LARYNGEAL NERVES DIVIDED (86 NERVES)

	No.	Per cent
Superior thyroid level	21	24.2
Thyroid level	47	54.7
Inferior thyroid level	18	20.9

tion between the gland and the nerve was not at the lower pole as is generally assumed, but rather at the postero-lateral surface at the junction of the middle and lower third, right at or just above the point where the chief branches of the inferior thyroid artery enter the gland." With this statement I am in full agreement. They further state that the nerve is often in extremely intimate relationship to the gland substance on the posterior surface of the thyroid, an observation which coincides with my own.

Berlin and Lahey (7) in 1929 reported on dissections of the recurrent laryngeal nerve, and Berlin (8) in 1935 published a further report on this structure. I am in disagreement with the concept that the recurrent laryngeal nerve penetrates the substance of the thyroid gland, having seen instances in which adenomas had grown around the main trunk of the nerve, but careful dissection proved that the nerve did not penetrate the gland substance proper, even though it was obviously in close relationship. Embryologically, it would seem impossible for the recurrent laryngeal nerve to traverse the gland parenchyma. I am, however, in agreement with these authors that the inferior cornu of the thyroid cartilage represents a good landmark for the location of the recurrent laryngeal nerve, since the nerve generally passes just posterior to this articulation.

It is very easy to miss the presence of a divided-trunk recurrent laryngeal nerve in the live patient during the course of operation. The surgeon, upon discovering a branch of the recurrent nerve trunk, naturally may presume that this is the nerve en toto and may terminate his search rather than lay open all the tissue spaces in the neck in search of a possible second or third branch. It is, therefore, only in the cadaver, where one can reach the entire area extending from the prevertebral fascia all the way anteriorly to the pretracheal fascia and extending also from a point behind the clavicle and first rib well up onto the thyroid cartilage, that one is able to demonstrate conclusively the presence or absence of a divided-trunk recurrent laryngeal nerve.

There are those who feel that the routine dissection of the recurrent laryngeal nerves at the time of operation is the best way to prevent damaging them. A knowledge of the wide variability of the branching pattern seems to justify the conclusion that it is only in the cadaver that a sufficiently wide dissection may be made to demonstrate the entire nerve. My dissecting-room experience clearly shows that one may be deceived into believing he has dissected out the entire recurrent laryngeal nerve, when actually he has exposed only one branch; further dissection would reveal the presence of one or more branches. It is not practical, therefore, when the primary mission of the operation is the removal of the thyroid gland, to make a dissection wide enough to isolate completely the recurrent laryngeal nerves.

Moreover, complete dissection of the recurrent laryngeal nerves for the purpose of avoiding damage to these structures, is attendant with a certain amount of troublesome bleeding, and it is impossible to carry out such a procedure without severance of multiple branches of the nerve to the trachea and esophagus. The importance of these small branches is problematical, but it seems difficult to justify their indiscriminate severance in order to expose completely all the component branches of the recurrent laryngeal nerve.

Nordland (9) states, contrary to the opinion of others, that there are no constant differences in relationship between the inferior thyroid artery and the recurrent laryngeal nerves. I agree with Nordland, to the extent that there are no constant differences in relationship which may be firmly depended upon in the performance of thyroid surgery (Table 5). One may find a nerve that has branched two or more times on one side, while finding

TABLE 5. RELATION OF BRANCHES OF RECURRENT LARYNGEAL NERVE TO BRANCHES OF INFERIOR THYROID ARTERY (200 NERVES)

	Anterior	Between	Posterior	Parallel
Right single-trunk nerves	19	9	18	10
Right divided-trunk nerves	17	17	20	8
Left single-trunk nerves	14	12	33	12
Left divided-trunk nerves	5	14	22	4
Total	*55*	*52*	*93*	*34*
Per cent	*27.5*	*26.0*	*46.5*	*17.0*

a single trunk on the other side. Furthermore, these branches or principal trunks may, and often do, intertwine between branches of the inferior thyroid artery; at one point they lie anterior to the artery, whereas only a centimeter or two away they lie directly posterior to it.

Single filaments of a recurrent laryngeal nerve with multiple branches are damaged more frequently than is supposed. These injuries usually remain undiagnosed, due to the fact that the function of the vocal cords has not been grossly interrupted and therefore the cords do not assume a position of paralysis which may be observed by laryngoscopy. However, the complaint of voice fatigue is probably indicative of such injuries.

The question might be reasonably asked at this time, "How does one avoid damage to an anatomic structure so obscure and so variable?" The best way to avoid damage to such a variable anatomic structure is for the surgeon to be aware of the multiple structural possibilities in the first place. It is self-evident that he cannot look at the neck of an individual and divine whether the recurrent laryngeal nerve has one or many branches

or whether it lies in front or in back of the inferior thyroid artery. If, however, the surgeon approaches the operation with a real appreciation of the presenting anatomy, he will proceed with dexterity and educated watchfulness. He will either stay away from danger areas or, realizing that he is in such an area, carry out his dissection in such a meticulous fashion as to avoid accidental bleeding, blind application of clamps and injudicious use of mounted sutures. Nevertheless, there will always be instances in which injury to the recurrent laryngeal nerve cannot be avoided.

Ligature of the inferior thyroid artery in selected cases, at a point as far lateral as possible, will lessen the possibility of accidental hemorrhage in the vulnerable area and the complications which so frequently result. The lateral ligature of the inferior thyroid artery should be carried out in an area where there is no likelihood of damage to the recurrent laryngeal nerve.

It cannot be recommended too strongly that all patients upon whom thyroid or neck surgery is contemplated, be subjected to preoperative and postoperative laryngoscopy. This is especially mandatory when the patient has had previous surgery of the neck. The medicolegal aspects of such a precautionary examination become clear when one sees malposition or malfunction of one or both vocal cords prior to surgery; the postoperative examination of the larynx and vocal cords is of equal importance.

SUMMARY

1. A study of 200 recurrent laryngeal nerves is presented. Of these nerves, 114 or 57 per cent had a single trunk, whereas 86 or 43 per cent had a divided trunk.

2. Recurrent laryngeal nerves with divided trunks were found to occur bilaterally in 24 per cent of the subjects examined.

3. The recurrent laryngeal nerve may branch at any point peripheral to its point of origin from the parent vagus nerve.

4. There is no consistency in the nerve pattern between right and left sides.

5. The point at which the recurrent laryngeal nerve is most vulnerable to injury is on the postero-lateral surface of the thyroid at the level of the junction of the middle and lower thirds, where the chief branches of the inferior thyroid artery usually enter the gland.

6. Secondary and tertiary divisions of the recurrent laryngeal nerve may occur extralaryngeally.

7. Injury to these secondary and tertiary divisions in this vulnerable area offers an adequate explanation for the more complex and heretofore controversial types of laryngeal paralyses.

8. Injury to one branch of a nerve with a divided trunk will produce

paralysis only in the area supplied by that branch. In some instances, only a single muscle or a portion of a muscle may be supplied by this branch.

9. The results of this study confirm the contributions made by Dr. Brien T. King.

Acknowledgments

We wish to extend our sincere thanks to Dr. William O. Reinhardt, Professor of Anatomy, University of California, Berkeley, and Dr. Donald Gray, Professor of Anatomy, Stanford University, for their kindness in making cadaver material available in this study; and to Mr. Ralph Sweet, Chief Medical Illustrator, University of California School of Medicine, for his excellent work in drawing the illustrations. We wish to thank especially Dr. John B. de C. M. Saunders, Professor of Anatomy and Chairman of the Division, University of California School of Medicine, for his generous assistance and contributions to this study.

REFERENCES

1. King, B. T., and Gregg, R. L.: An anatomical reason for the various behaviors of paralysed vocal cords, *Ann. Otol., Rhin. & Laryng.* **57:** 925 (Dec.) 1948.
2. King, B. T.: A new and function restoring operation for bilateral abductor cord paralysis, *J.A.M.A.* **112:** 814 (Mar.) 1939.
3. Negus, V. E.: Certain anatomical and physiological considerations in paralysis of the larynx, *Proc. Roy. Soc. Med.* **40:** 849 (Dec.) 1947.
4. Negus, V. E.: The Mechanism of the Larynx. St. Louis, C. V. Mosby Co., 1929.
5. Murtagh, J. A., and Campbell, C. J.: Respiratory function of the larynx. III. The relation of fiber size to function in the recurrent laryngeal nerve, *Laryngoscope* **61:** 581 (July) 1951.
6. Fowler, C. H., and Hanson, W. A.: Surgical anatomy of the thyroid gland with special reference to the relations of the recurrent laryngeal nerves, *Surg. Gynec., & Obst.* **49:** 59 (July) 1929.
7. Berlin, D. D., and Lahey, F. H.: Discussions of the recurrent and superior laryngeal nerves, *Surg. Gynec., & Obst.* **49:** 102 (July) 1929.
8. Berlin, D. D.: The recurrent laryngeal nerves in total ablation of the normal thyroid gland, *Surg. Gynec., & Obst.* **60:** 19 (Jan.) 1935.
9. Nordland, M.: The larynx as related to surgery of the thyroid based on an anatomical study, *Surg. Gynec., & Obst.* **51:** 449 (Oct.) 1930.

Letters to the Editor

NEW PHARMACOLOGIC PROPERTY OF QUINIDINE: PROTEIN ANABOLIC EFFECT*†

To the Editor:

Quinidine and its levo-isomer quinine are undoubtedly the two most important derivatives of cinchona bark. Their many biologic and therapeutic properties are said to differ only quantitatively. Both are "general protoplasmic poisons"; quinidine is considered somewhat less toxic to unicellular organisms (1).

Stereoisomerism about the secondary alcohol linkage between the quinoline and quinuclidine rings does not alter plasmocidal activity significantly (2). However, qualitative distinction based on the isomerism of these two drugs may explain the observation that idiosyncrasy to quinine often extends to other levorotatory cinchona alkaloids, but rarely to the dextrorotatory compounds (3). As another qualitative difference between these two substances, therefore, it is of considerable interest to report our observation that quinidine sulfate, when administered by mouth, has a protein anabolic effect which is not shared by quinine sulfate when administered in the same manner.

Human metabolic balance techniques described by Reifenstein *et al.* (4) were used in this study. Nitrogen was determined by macro and micro Kjeldahl methods and urinary 17-ketosteroids by extraction with carbon tetrachloride in acidified urine and subsequent colorimetric determination using aqueous potassium hydroxide and a dehydroepiandrosterone standard. The urinary nitrogen was determined on 3-day pools, the fecal nitrogen on 6-day pools. The diet was constant throughout. The balance periods were six days in length.

The subject was a 67-year-old female with nutritional and postmenopausal osteoporosis and severe kyphoscoliotic thoracic deformity. She was on a metabolic balance regimen designed to evaluate the effects of long-acting testosterone esters (5). Although there was a history of paroxysmal cardiac arrhythmia occurring twenty years previously, for which the

* Publication No. 34 of the Oklahoma Medical Research Foundation.

† This investigation was supported in part by research grants from the National Institute of Arthritis and Metabolic Diseases (A-179) and the National Heart Institute (H-1429) of the National Institutes of Health, Public Health Service.

patient had been given digitalis for approximately one year, no cardiovascular abnormality was noted on physical examination, and no arrhythmia was observed during the first four months of study. Shortly thereafter, auricular fibrillation developed following three or four days of numerous extrasystoles. Since the patient was still showing some effect from one of the testosterone preparations, specific therapy was withheld for several days until mild congestive failure developed. Then quinidine sulfate, 0.2 gram, was administered every two hours until a normal sinus mechanism supervened shortly after a total of 1 gram had been administered. She was given thereafter a maintenance dose of 0.2 gram three times daily. Infrequent bouts of paroxysmal fibrillation occurred with this dose but the arrhythmia eventually disappeared and the quinidine was discontinued after three weeks, without recurrence of the arrhythmia. The balance data are charted in the accompanying graph (Fig. 1). The patient had experienced a prolonged protein anabolic effect from an injection of testosterone phenylacetate given thirty days previously and the nitrogen balance was approaching the control level when fibrillation developed. It was discovered that a definite protein-anabolic effect had been induced by the quinidine. There was a prompt decrease in urinary nitrogen excretion and gain in body weight. The first 3-day portion of balance period #20 was marked by one day of anorexia, nausea and some vomiting, resulting in a decreased

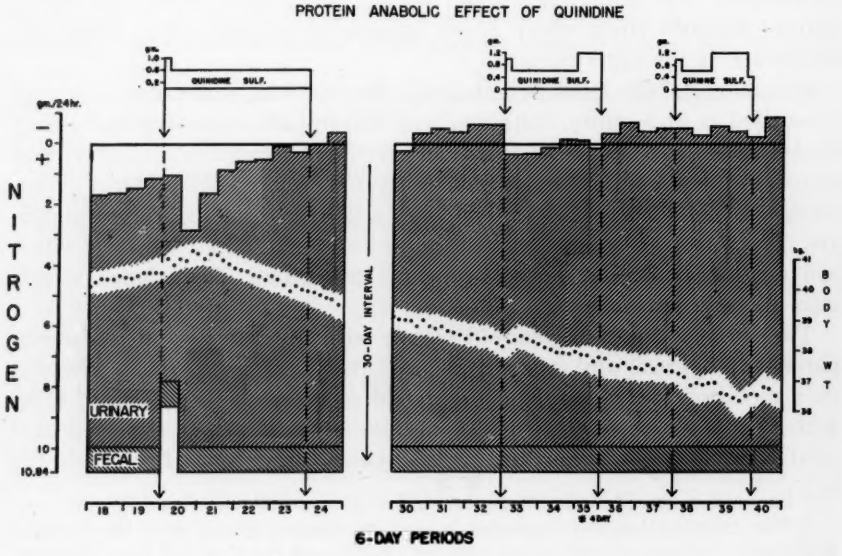


FIGURE 1

nitrogen intake for the pool period. By the end of balance period #21 the nitrogen excretion had resumed its pre-quinidine level.

In order to exclude the possibility that the positive nitrogen balance induced by the previously administered testosterone might have influenced the metabolic effect of quinidine, and to rule out any effect attributable to the conversion from fibrillation to a sinus mechanism, the patient was studied again at a time when she was not under the influence of a testosterone preparation, was in nitrogen equilibrium, and was without cardiac arrhythmia. The same dosage schedule was employed. After twelve days of therapy, the daily quinidine dose was increased to 1.2 grams. This second period of quinidine administration, beginning with balance period #33 (during which time the nitrogen balance data were available on a daily basis), was characterized by prompt reversal in nitrogen balance from a mean loss of 0.42 gram of nitrogen daily during the three periods (eighteen days) prior to quinidine (periods #30, #31 and #32) to an average daily nitrogen retention of 0.55 gram during the six days included in period #33, an average net gain of almost 1 gram of nitrogen daily. There was noted again a slight increase in body weight. Thereafter, nitrogen excretion increased until the dose of quinidine was doubled, whereupon nitrogen excretion decreased briefly and quinidine was then discontinued. The phosphorus balance data show a similar pattern, but the calcium balance data show no significant change.

Subsequently, and at a time when the patient had been without treatment and in a state of nitrogen equilibrium for several days, quinine sulfate was administered in comparable dosage (Fig. 1). The balance data for these periods (#38, #39 and #40) fail to reveal a significant effect on nitrogen metabolism attributable to quinine. This is in keeping with the observations of Hardiker (6, 7).

The urinary 17-ketosteroid excretion during these periods did not show any deviation attributable to either quinidine or quinine.

These observations have been verified in 2 subsequent subjects, and a more comprehensive study of this heretofore undescribed effect of quinidine is under way.

This unexpected effect of quinidine sulfate may be of importance for several reasons: 1) it may provide further insight into the mechanism of the cardiovascular effects of quinidine, 2) it reveals a protein-anabolic action of an organic compound with a chemical structure differing from compounds with known protein-anabolic activity and thereby may provide a starting point for the development of other new compounds with this activity, and 3) it may lead to a further understanding of the process of protein anabolism.

Quinidine sulfate in relatively small oral doses appears to possess a protein anabolic effect. This effect is not apparent when equivalent doses of quinine sulfate are administered under comparable circumstances.

ROBERT H. FURMAN, M.D.
R. PALMER HOWARD, M.D.
EDWARD C. REIFENSTEIN, JR., M.D.
Oklahoma Medical Research Foundation,
825 N. E. 13th Street,
Oklahoma City 4, Oklahoma

REFERENCES

1. GOODMAN, L., and GILMAN, A.: The Pharmacological Basis of Therapeutics. New York, The Macmillan Co., 1941.
2. VON OETTINGEN, W. F.: The Therapeutic Agents of the Quinoline Group. New York, Chemical Catalog Co., 1933.
3. DAWSON, W. T., and GARBADE, F. A.: Idiosyncrasy to quinine cinchonidine ethyl hydroxy cupreine and other levorotatory alkaloids of cinchona series; preliminary report, *J.A.M.A.* **94**: 704–705, 1930.
4. REIFENSTEIN, E. C., JR.; ALBRIGHT, F., and WELLS, S. L.: The accumulation, interpretation, and presentation of data pertaining to metabolic balances, notably those of calcium, phosphorus, and nitrogen, *J. Clin. Endocrinol.* **5**: 367–395, 1945.
5. HOWARD, R. P.; REIFENSTEIN, E. C., JR.; COURTRIGHT, C. L., and TURNER, H. H.: The prolonged anabolic activity of certain testosterone esters in man (abstract), *J. Clin. Endocrinol. & Metab.*, **13**: 832, 1953.
6. HARDIKAR, S. W.: Action of quinine on protein metabolism, respiratory exchange and heat function: protein metabolism, *J. Pharmacol. & Exper. Therap.* **23**: 395–448, 1924.
7. HARDIKAR, S. W.: Action of quinine on protein metabolism, respiratory exchange and heat function: respiratory exchange and heat function, *J. Pharmacol. & Exper. Therap.* **25**: 175–218, 1925.

GROSS INACCURACY OF CERTAIN COLOR REACTIONS CONSIDERED SPECIFIC FOR DEHYDROEPIANDROSTERONE AND DERIVATIVES IN URINE EXTRACTS

TO THE EDITOR:

The September 1953 issue of the JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM contains an article by Dr. Lytt I. Gardner entitled "Urinary Dehydroepiandrosterone in Idiopathic Hirsutism: Influence of Cortisone Therapy." In his excellent studies, Dr. Gardner made the assumption that the Allen-reactive chromogens contained in neutral extracts from strong acid-hydrolyzed urines actually are chiefly dehydroepiandrosterone and certain of its derivatives. In this respect, his paper is representative of an increasing body of clinical endocrine literature in which the assumption is made that urinary dehydroepiandrosterone (DHA) and cer-

tain of its derivatives can be dependably estimated by the use of one of the supposedly specific color reactions, such as the modified Pettenkofer reaction or the Allen "blue" test.

The impression that these color reactions can be used to estimate the DHA steroids unfortunately is incorrect, as I shall indicate. Lest it seem that this statement is a criticism of Dr. Gardner's and other investigators' careful work, the writer also has been guilty of this particular misinterpretation (1, 2).

In general, the supposedly specific color reactions have had the following considerations favorable to a belief in their specificity. 1) In normal adults, the color/Zimmermann ratios of the crude neutral fractions are of the same general order of magnitude as the DHA/Zimmermann ratios obtained by techniques which give minimal destruction of DHA. 2) When the color values increase, the digitonin-precipitable beta-ketonic steroids generally increase. There is a widespread impression that the composition of the beta-ketonic fraction is rather well known and that DHA has been shown to constitute most of this fraction. This impression appears incorrect, except in the case of untreated normal nonpregnant adults and certain patients with malignant adreno cortical tumors. In these particular urines, there is no reason to doubt that DHA probably is the predominant steroid in the beta-ketonic fraction. This has not been shown for any other condition in which the output of "color test" reactive steroid has a marked increase; indeed, as I shall indicate, DHA is not the predominant beta-ketonic steroid in any of these other conditions in which Allen or Pettenkofer chromogens show a marked increase. 3) The spectrophotometric curves of the color given by isolated beta-ketonic fractions in the color reactions have been found to be closely similar to the curve obtained with authentic samples of DHA. This finding indicates that the chromogenic material in the beta-ketonic fraction *might be* DHA; it does not indicate that it actually is DHA. Spectrophotometric curves of color reactions vary in specificity; uric acid and resorcinol give indistinguishable curves in the urea-cyanide intensified arsenophosphotungstate reaction.

It cannot be denied that the foregoing findings are highly suggestive but, on the other hand, it is apparent that there are loopholes.

I should now like to review the findings, partly from the writer's laboratory and partly from others, with regard to the relationship between urinary DHA and derivatives and the apparent values obtained by "specific" color tests in a number of situations in which the output of color test chromogens is markedly increased.

1. *Malignant adrenal tumors.* A number of isolation studies on patients excreting large amounts of chromogen or large amounts of beta-ketonic steroid have been made. So far as the writer is aware, DHA and its deriva-

tives have always been isolated in satisfactory amounts in such cases. For example (through the cooperation of Dr. G. W. Bissell) we recently had the opportunity to study the urine of a patient with metastatic feminizing adrenocortical carcinoma and marked hyperestrogenuria. This patient's Pettenkofer/Zimmermann ratio was 0.93, and paper chromatograms showed that increased DHA excretion was largely responsible for the elevation.

2. *Dehydroepiandrosterone administration.* There can be little objection to equating the increased output of chromogens with an increased excretion of DHA and derivatives.

3. *Corticosterone administration.* DHA is used as the standard both in the "specific" color tests and for the Zimmermann reaction in our and most other laboratories. Therefore, if all the urinary steroid consisted of DHA, the color/Zimmermann ratio could not possibly exceed 1.0. Unfortunately, normal and adrenalectomized adults given 200 or more milligrams per day of intramuscular or oral corticosterone regularly have an increase in the Pettenkofer/Zimmermann ratio from its usual value of 0.25–0.35 to values in excess of 1.0, occasionally in excess of 2.0. The *extra* steroids excreted almost always have a Pettenkofer/Zimmermann ratio above 2.0. Therefore DHA cannot be an important constituent of the chromogens excreted after corticosterone administration.

Direct confirmation of this view has been obtained by column chromatography in Dr. Jailer's laboratory and by paper chromatography in our laboratory. Although the beta-ketonic steroid output increases considerably in a normal adult given corticosterone, the DHA output is less than that under basal conditions. The increase is due to a highly polar beta-ketonic steroid designated PC1, and somewhat smaller amounts of other steroids. In addition the urine contains very large amounts of two alpha-ketonic color-reactive steroids, PC2 and PC3.

4. *Corticotropin administration.* The marked increase in Allen or Pettenkofer chromogens is not accompanied by a similar increase in DHA output. Chromatograms of the urinary steroids show marked increases in PC1, PC2 and PC3 while DHA either remains constant or shows a much smaller increase. The former three groups are the chief source of the increased output of chromogens; the pattern is similar to that seen when corticosterone is given.

5. *Premature infants.* About 40 per cent of the urines of untreated premature infants were found by Eagle to give positive qualitative results with the Allen "blue" test. The frequency of positive responses was unchanged when 25 mg. of intramuscular cortisone was administered for a day or two but 100 per cent of the urines gave positive results when the children were given 10 units per day of long-acting ACTH. Quantitative values were consistent with these findings. The Allen/Zimmermann ratio in the un-

treated infants had a median of 0.52—almost ten times that of normal adults—and it rose to a median of 0.84 during ACTH administration. The Pettenkofer/Zimmermann ratio also was about ten times as high as in normal adults. The original interpretation of these findings was that infants excreted large amounts of DHA and that ACTH stimulated excretion of this steroid (3).

A simple finding which emerged from a review of his data convinced Dr. Eagle that this interpretation was probably incorrect. The *extra* steroid excreted by babies given ACTH had a median calculated Allen/Zimmermann ratio of 1.8 but, even if it had been entirely DHA, the expected ratio could not have exceeded 1.0.

Cooperative studies carried out by our laboratory, with Dr. Eagle's help, have fully justified his skepticism regarding the original interpretation. In the first studies, all crude neutral fractions prepared from urines which gave positive results with the Allen "blue" test were mixed together to give one large pool which had a Pettenkofer/Zimmermann ratio above 1.0. No DHA could be detected in paper chromatograms either of the pooled crude neutral extract or in the fractions prepared by using Girard's reagent T and digitonin. At least for the first few hours after color development, the chromatograms contained the three PC spots seen after corticosterone is given to adults and were indistinguishable from strips prepared from the urine of adults given this steroid. Later, the beta-ketonic fraction developed a previously unobserved spot, PC4, which, unlike the other three, moved faster (less polar) than DHA and which, from its R_{DHA} of 2.0–2.2, may be an artifact.

6. *Pregnancy.* Patients followed through pregnancy show a marked increase in Pettenkofer chromogen excretion without significant increases in Zimmermann chromogen excretion. The ratio of Pettenkofer/Zimmermann is appreciably above the control at the end of the first trimester and is twice to three times the control, usually 0.75 to 1.00, by the middle of the last trimester. Paper chromatography has shown some increase in DHA, but the increase is far too small to be a full explanation. The major cause of the increased output of chromogens appears to be a striking increase in the output of the highly-polar beta-ketonic PC1 steroid, without similar increases in PC2 or PC3. 11-Keto-progesterone is able to cause a similar increase in Pettenkofer chromogen excretion but progesterone does not. Since there is increasing evidence of the secretion of 11-oxygenated steroids by the placenta, the possible role of the former steroid in the changes in urinary steroid pattern is being studied.

Detailed reports of the foregoing findings will be published later.

* * *

Since this letter is largely concerned with data relating to DHA, it may

be well to correct an error which has appeared in a recent review, not because of any fault of the reviewers, but because the original statements were abstracts and therefore necessarily truncated in style. Abstracts presented at the 1952 meeting of The Endocrine Society seemed to state that Munson, Labhart and Forsham found cortisone and hydrocortisone to be precursors of urinary Pettenkofer chromogen (4), whereas our group had not observed such an increase (1).

Actually, both groups had similar findings. Administration of either steroid to an adrenalectomized man caused some small increase in Pettenkofer chromogen excretion but a large increase in Zimmermann chromogen. A patient so treated has a Pettenkofer/Zimmermann ratio far below that of normal adults, whereas an adrenalectomized patient given corticosterone has a ratio far above that of normal adults.

However, when cortisone or hydrocortisone is given to normal adults, an actual decrease in Pettenkofer output does gradually occur. This obviously means that the Pettenkofer chromogen which is produced from the administered steroids is not sufficient to compensate fully for the decrease in Pettenkofer excretion which results from inhibition of adrenal cortical activity secondary to steroid inhibition of endogenous ACTH output.

The actual source of the apparent discrepancy was that an almost exactly identical output of Pettenkofer chromogen was referred to as a significant increase by one group, but considered a "trifling increase" by the other group (5).

* * *

It is apparent from the findings summarized earlier in this letter that measurement of Allen blue chromogens, Pettenkoffer chromogens, and probably all chromogens involved in similar color reactions, is not a reliable means of estimating urinary dehydroepiandrosterone and derivatives, even though a fortuitous parallelism exists between the two sets of values in basal normal adults and in patients with certain malignant adrenal tumors. It should be noted that gravimetric or colorimetric estimation of the beta-ketonic fraction is equally unreliable, because we have seen all variations, ranging from samples in which this fraction is entirely PC chromogen to samples in which it is essentially entirely DHA. Therefore, Venning's older report of increased beta-ketonic steroid after ACTH may not be taken to demonstrate increased DHA excretion. What are the justifiable interpretations of a high Allen/Zimmermann or a high Pettenkofer/Zimmermann ratio? In the nonpregnant individual, experience supports Landau's impression that these chromogens are exclusively adrenocortical metabolites. However, the increased chromogen output may be chiefly DHA and derivatives (precursor unknown) or PC steroids which

are metabolites of corticosterone; mixtures of these patterns may also occur. Paper chromatography permits a rapid and relatively simple differentiation of these two known possibilities; but future work may show that there are other causes. However, the physiologic increase in the Pettenkofer/Zimmermann ratio which is seen in normal pregnancy may be either of adrenocortical or placental origin. It does not result from increased secretion of progesterone, however. Because the error of regarding Allen chromogens, Pettenkofer chromogens, or beta-ketonic steroids as measures of DHA has become widespread in recent endocrine literature, readers should be particularly careful to consider the specificity of the determinative methods, most critically when studying reports concerned with the excretion or precursors of dehydroepiandrosterone.

It is a pleasure to acknowledge and to thank Drs. Jailer, Eagle, Munson and Savard for the assistance which their advice and cooperation gave our studies.

WILLIAM Q. WOLFSON, M.D.

The Unit for Metabolic Research,
Department of Internal Medicine,
Wayne University College of Medicine,
Detroit 26, Michigan

REFERENCES

1. WOLFSON, W. Q.; EYA, M., and ROBINSON, W. D.: Human corticosterone metabolism. I. Corticosterone the principal precursor of urinary neutral Pettenkofer chromogens (dehydroepiandrosterone and derivatives), (abstract) *J. Clin. Endocrinol. & Metab.* **12**: 970, 1952.
2. WOLFSON, W. Q.; CHAMBLISS, M., and ROBINSON, W. D.: Human corticosterone metabolism. III. The urinary Pettenkofer chromogen increased by corticotropin or corticosterone is not dehydroepiandrosterone, (abstract) *J. Clin. Endocrinol. & Metab.* **13**: 851, 1953.
3. EAGLE, J. F.: Dehydroepiandrosterone and similar substances in urine of premature infants, *Proc. Soc. Exper. Biol. & Med.* **81**: 571, 1952.
4. MUNSON, P. L.; LABHART, A., and FORSHAM, P. H.: Cortisone and hydrocortisone as precursors of urinary dehydroepiandrosterone, (abstract) *J. Clin. Endocrinol. & Metab.* **12**: 969, 1952.
5. LIEBERMAN, S., and TEICH, S.: Metabolic precursors of urinary dehydroisoandrosterone (Editorial), *J. Clin. Endocrinol. & Metab.* **13**: 1140, 1953.

EFFECT OF ASCORBIC ACID ON HORMONAL EXCRETION

TO THE EDITOR:

Bacchus has reported that the administration of ascorbic acid to rats depresses the urinary excretion of 17-ketosteroids (1). Kayahan reported a 36 per cent decrease in 17-ketosteroid excretion coupled with an increase

in the excretion of 11-oxysteroids of 110 per cent when humans received 4 Gm. of ascorbic acid for four days (2). Goldzieher, however, could find no such changes in human subjects (3). We, too, were unable to find any significant change in urinary excretion of 17-ketosteroids and 17, 21-dihydroxy-20-ketosteroids when ascorbic acid in doses of 1.5–5.0 Gm. per day was given to 4 normal adults and to 4 children, 15, 13, 11 and 4 years of age. The children were in the hospital for elective surgery or for the investigation of convulsive disorders. Circulating compound F was also measured and bioassays for androgens were carried out. These showed no significant changes.

The only consistent change found was a sharp decrease in the urinary content of material giving the Allen blue color reaction. These findings are shown in Table 1.

TABLE 1. CONTROL* EXCRETION – EXCRETION WITH TREATMENT / CONTROL* EXCRETION

Patient	17-Ketosteroids %	17,21-Dihydroxy-20-ketosteroids %	"Blue chromogens" %
CO, male, 32 yrs.	− 6	− 7	−34
RO, male, 32 yrs.	−10	+35	−33
CO, female, 30 yrs.	− 4	− 2	−70
WA, male, 24 yrs.	0	+20	−58
MA, female, 11 yrs.	−32	0	−54
LA, male, 15 yrs.	−15	−20	−44
WI, male, 13 yrs.	− 5	0	−55
MI, male, 4 yrs.	+40	+17	−71

* Average excretion for pre-control and post-control periods.

It should be noted that in the 3 adults given ascorbic acid for four days there was a disappearance of the effect on the "blue chromogens" by the last day of treatment. The other patients received ascorbic acid only from one to two days.

ROBERT KLEIN, M.D.
CONSTANTINE PAPADATOS, M.D.
JAMES FORTUNATO, M.S.

The Department of Pediatrics,
Children's Hospital of Pittsburgh, and
The University of Pittsburgh Medical School,
Pittsburgh 13, Pennsylvania

REFERENCES

1. BACCHUS; H.; ALTSZULER, N., and HEIFFER, M. H.: Decreased excretion of cortisone

metabolites immediately following ascorbic acid treatment, *Endocrinology* **51**: 302, 1952.

2. KAYAHAN, S.: Effect of high doses of ascorbic acid on adrenal function, *J. Endocrinol.* (British) **8**: 211, 1952.
3. GOLDZIEHER, J. W., and EDLIN, J. S.: The effect of orally administered ascorbic acid and/or *l*-cystine on urinary steroid excretion, *J. Clin. Endocrinol. & Metab.* **13**: 436, 1953.

TESTOSTERONE THERAPY FOR FRACTURES AND CERTAIN MALIGNANT AND NONMALIGNANT BONE CONDITIONS

TO THE EDITOR:

The effects of male sex hormones on fractures of bone (especially in the aged), on osteoporosis, and on some other malignant and nonmalignant bone conditions have been investigated by the authors at St. Giles' hospital (London) in a series of 34 cases. This study was undertaken because of favorable results claimed by Mosti (1) in Italy; by Hagenbach (2), Debrunner (3), Schmid (4), and Fredenhagen (5) in Switzerland; and by Davis (6) and Reifenstein and Albright (7) in the United States.

Most workers believe that testosterone acts by restoring the imbalance between protein-building nitrogen hormones (N) and the sugar-building hormones (S) observed after severe fractures and in senile osteoporosis, and characterized by qualitative and quantitative protein deficiency of the bony matrix.

Testosterone propionate (50–100 mg. intramuscularly daily) and lingual tablets of methyltestosterone (25 mg. from one to four times daily) were used. The treatment was purely empirical, and the total dosage varied considerably. Most cases required much larger doses than those recommended by Mosti (1) in his original paper.

The average age in this series was 55.6 years. The preponderance of women (22 female and 12 male patients) was incidental.

RESULTS AND CONCLUSIONS

1. Striking effects on muscle tone, skin, blood tissues and morale were observed, particularly in senile patients. Undesirable effects (such as hirsutism, voice changes, edema and acne) were few and of a minor nature.

2. Most cases showed a notable increase in the level of serum alkaline phosphatase, and the urinary 17-ketosteroid excretion. There was also an increase in the erythrocyte count and hemoglobin percentage, in patients who had microcytic anemia.

3. A mixed selection of fractures (26 fractures in 22 patients, mostly elderly) was treated. Hormone therapy was combined with standard or-

thodox procedures. In most of the cases the average expected healing time was shortened. (Example: male, aged 58, with three fractures in the same leg—base of neck and shaft of femur, and mid-tibia. Treatment: plaster fixation and testosterone propionate, 100 mg. i.m. daily for six weeks. Union occurred, with a massive callus, allowing weight-bearing at six weeks.) Radiologic evidence of early callus formation in most of the cases was not as marked, however, as claimed by Mosti and others. Fractures of the neck of the femur responded well to a combination of nailing and testosterone. Good results were achieved in several cases of non-union, especially in one case of ununited compound fracture of the tibia with chronic osteomyelitis.

4. Routine administration of male hormone is recommended in all elderly people of *both sexes* with fractures and general osteoporosis: a) to achieve early union; b) to avoid delay or non-union; c) to save on the occupancy of valuable hospital beds.

5. Four of 5 cases of Paget's disease with pathologic fractures had early union and marked relief from pain.

6. Regeneration occurred in an enchondroma of the finger with pathologic fracture; this process was accompanied by remineralization of osteoporotic phalanges (female, aged 41).

7. Radiographic evidence of remineralization in senile osteoporosis was inconclusive. Bone biopsies suggested increased osteoblastic activity during testosterone therapy.

8. Rapid healing of the patella and tibial tuberosity was observed in a case of osteochondritis juvenilis (8).

9. Several cases of mammary carcinoma with skeletal metastases improved greatly. Radical mastectomy with massive and prolonged testosterone therapy is regarded as the method of choice (9, 10). A temporary improvement was observed in a carcinoma of the thyroid with bony metastases.

10. The present series is too small to allow final judgment on this form of therapy. The results must be regarded with caution until larger series with controls have been studied in other centers.

J. Wolf, M.B., B.Ch., L.M.*
A. A. Loeser, M.D.†

REFERENCES

1. Mosti, R.: L'azione dell'ormone testicolare sulla consolidazione delle fratture nei vecchi, *Ann. ital. chir.* **18**: 281, 1939.
2. Hagenbach, E.: Perandren bei schlechter Kallusbildung, *Schweiz. med. Wchnschr.* **71**: 1212, 1941.

* Late Surgical Registrar, St. Giles' Hospital, London, England. Present address: c/o Director of Medical Services, Penang, Malaya.
† London, England.

3. DEBRUNNER, H.: Ueber die Verwendung von Perandren bei Erkrankungen am Skelettsystem, *Schweiz. med. Wchnschr.* **75**: 947, 1945.
4. SCHMID, H.: Zur Beeinflussung der Kallusbildung durch Perandren (Ciba), *Schweiz. med. Wchnschr.* **76**: 538, 1946.
5. FREDENHAGEN, H.: Die Wirkung von Perandren auf die Epiphysen, *Schweiz. med. Wchnschr.* **78**: 16, 1948.
6. DAVIS, J. W.: Treatment of recent intracapsular fractures of the neck of the femur, *Indust. Med.* **2**: 423, 1942.
7. REIFENSTEIN, E. C., JR., and ALBRIGHT, F.: The metabolic effects of steroid hormones in osteoporosis, *J. Clin. Invest.* **26**: 24, 1947.
8. WOLF, J.: Larsen-Johansson disease of the patella. Seven new case records. Its relationship to other forms of osteochondritis. Use of male sex hormones as a new form of treatment, *Brit. J. Radiol.* **23**: 270, 1950.
9. LOESER, A. A.: Male hormone in gynaecology and obstetrics and in cancer of the female breast, *Obst. & Gynec. Survey* **3**: 363 (June) 1948.
10. ADAIR, F. E.: Use of irradiation, surgery and hormones in breast cancer, *Proc. Roy. Soc. Med.* **42**: 468, (July) 1949.

EFFECT OF DCA ON HEMODYNAMICS AND ELECTROLYTE BALANCE OF NORMAL PREGNANT WOMEN

TO THE EDITOR:

In this *Journal* Assali, Clark and Sobel (1) published data concerning the effect of DCA administered to 5 normotensive pregnant women. In 4 DCA and salt, in the amounts used, had no effect on weight, blood pressure or sodium balance.

Analysis of the data from the clinical experiments of Dieckmann (2) reveals that DCA administered to patients with toxemia of pregnancy has little effect, if any, on weight, blood pressure, sodium balance and urinary protein, especially if salt is given at the same time. In nonpregnant individuals a much more definite effect of the same amounts of DCA and salt is to be expected.

In addition to circumstantial evidence (3, 4) for the activity of sodium-retaining steroids of placental origin in toxemia, I should like to suggest that the relatively minimal effect of DCA and salt in pregnant women, especially in patients with toxemia, points to the fact that, in these circumstances, already a heightened activity of DCA-like factors is present. As a consequence the amounts of DCA administered, although high (absolutely) for nonpregnant women, are relatively low for pregnant women, especially when toxemia exists.

J. L. MASTBOOM, M.D.

Department of Obstetrics and Gynecology,
University of Amsterdam,
The Netherlands

REFERENCES

1. Assali, N. S.; Clark, L. C., Jr., and Sobel, E. H.: Studies on toxemia of pregnancy: effect of desoxycorticosterone acetate (DCA) on hemodynamics and electrolyte balance of normal pregnant women, *J. Clin. Endocrinol. & Metab.* **13**: 1030, 1953.
2. Dieckmann, W. J.: The Toxemias of Pregnancy ed. 2. St. Louis, The C. V. Mosby Company, 1952, p. 357–361.
3. Mastboom, J. L.: The importance of adrenocortical steroids for the development of toxaemia of late pregnancy, *Gynaecologia* **134**: 217, 1952.
4. Mastboom, J. L.: Plazentare Kortikosteroide und ihre Bedeutung für die Entstehung der Spättoxikose der Schwangerschaft, *Zentralbl. f. Gynäk.* **75**: 801, 1953.

METABOLIC EFFECTS OF "PITUITARY GROWTH HORMONE PREPARATIONS" IN HUMAN SUBJECTS

SUMMARY OF QUANTITATIVE STUDIES EXTENDING OVER A FIVE-YEAR PERIOD

To the Editor:

In 1945, Young reported that the administration of a partially fractionated pituitary extract, rich in growth hormone, produced significant protein anabolism (1). In the ensuing years, Li (2), Wilhelmi (3) and others have prepared "highly purified" pituitary materials which are reported to have a significant and consistent growth effect in hypophysectomized rats. The literature covering a portion of the field (to 1948) has been reviewed by Li and Evans (4).

Beginning in 1948, in addition to ourselves, several groups of investigators including Shorr, Kenyon, Wilkins, Albright, and their respective collaborators, began evaluating these "highly purified" preparations in human subjects under controlled metabolic conditions. In this report will be presented the results of such studies in this laboratory during the period 1948 to 1953.

METHODS

The chemical procedures and the techniques used in the performance of the balance studies were those employed routinely in this laboratory (5). Subsequent to the year 1951, mixed diets were supplanted by diets prepared according to formulae, as described by Olson *et al.* (6); this made for constancy in a quantitative chemical sense.

OBSERVATIONS

During the period 1948–1949, two "highly purified growth hormone preparations" prepared by Dr. Choh Hao Li of the University of California were tested by us in human subjects. These preparations caused pyrexia

and produced nitrogen loss, with no increase in 17-ketosteroid excretion (Fig. 1). Similar preparations used by other investigators during the same period resulted in similar findings.

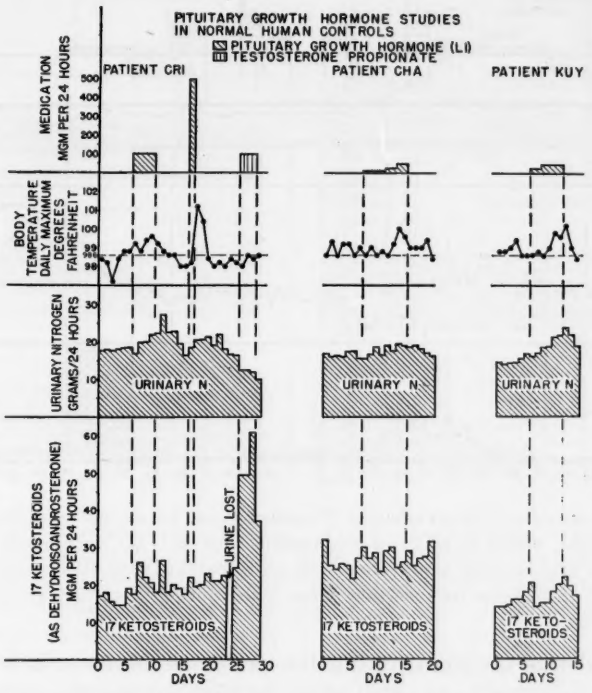


FIG. 1. Hyperpyrexia and increased nitrogen excretion in 3 normal male patients during administration of "pituitary growth hormone" (1948 studies). Hyperglycemia resulted in Patient CRI during the administration of 500 mg. of "pituitary growth hormone" per day. Testosterone produced its characteristic anabolic response in this patient.

During the period 1949–1950, a "growth hormone preparation" prepared by Dr. Hays and his associates of the Armour Laboratories was tested in a patient with panhypopituitarism. Lack of effect or actual net loss of the constituents of protein tissue and bone was observed (Fig. 2).

In 1952, two growth hormone preparations were tested in a patient with no endogenous thyroid function. One was prepared by Drs. Hays and Steelman and their associates, and the other by Dr. Li. The material was administered by slow intravenous drip during approximately half of each 24-hour period, for sixteen days. No pyrexia resulted. Furthermore, for the first time in our experience a significant retention of nitrogen, potassium

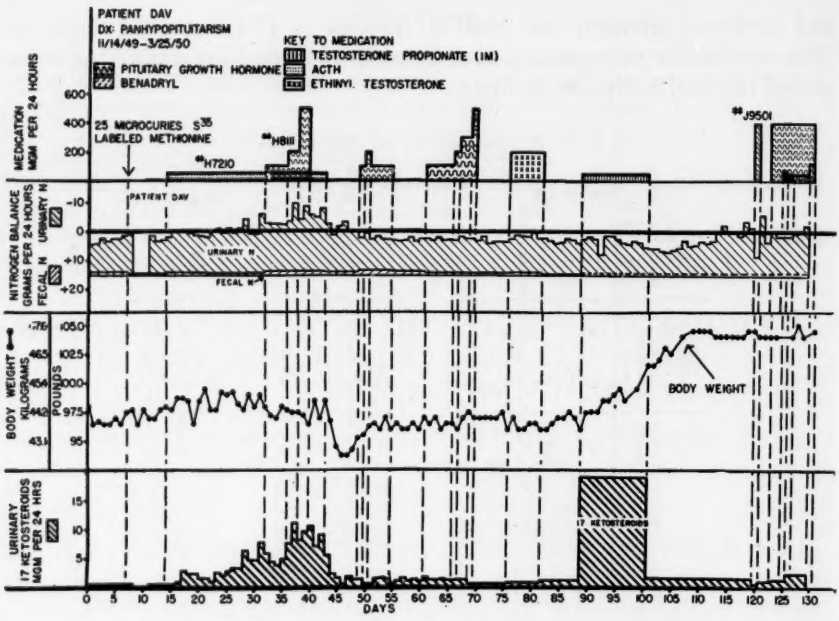


FIG. 2. Lack of significant effect of "pituitary growth hormone" on nitrogen balance or body weight, either alone or in conjunction with ACTH. No pyrexia occurred. In contrast, the anabolic effects of testosterone are apparent (1949–1950 studies). Negative calcium and phosphorus balances also were noted during "pituitary growth hormone" administration.

and phosphorus occurred during the period of hormone administration and some "rebound" was noted when the hormone was discontinued (Figs. 3a and 3b). Weight gain, which was more than proportional to the nitrogen retention, suggested some fluid retention, perhaps referable to pituitary antidiuretic factor. Lack of sodium retention, of increase in 17-ketosteroid excretion, or of a significant fall in eosinophils indicated that there was little or no ACTH contamination.

In 1952, 3 patients received "pituitary growth hormone" prepared by Drs. Raben, Westermeyer, and Astwood, and by Drs. Hays and Steelman of the Armour Laboratories, respectively. Both lots of material were prepared by column fractionation, as reported by Raben and Westermeyer (7). Except for some phosphorus retention, the material prepared by Dr. Raben produced no consistent effect at any dosage level used. Unfortunately, urinary and fecal calcium were not determined. The material prepared by the Armour group appeared to be rather heavily contaminated with corticotropin, and induced the metabolic changes characteristic of such material (Figs. 4, 5 and 6).

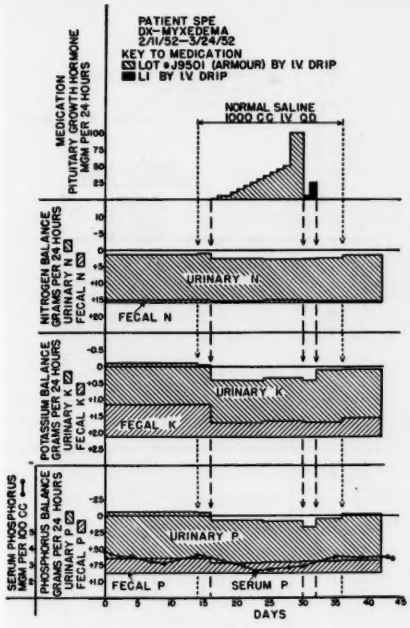


FIG. 3a. Apparent retention of nitrogen, potassium and phosphorus during administration of "pituitary growth hormone" to a patient with myxedema. There was a gain in weight during the pretreatment control period (3 pounds) and during treatment with Armour's "pituitary growth hormone" (9 pounds). A weight loss of 4 pounds occurred following the omission of Armour's "pituitary growth hormone."

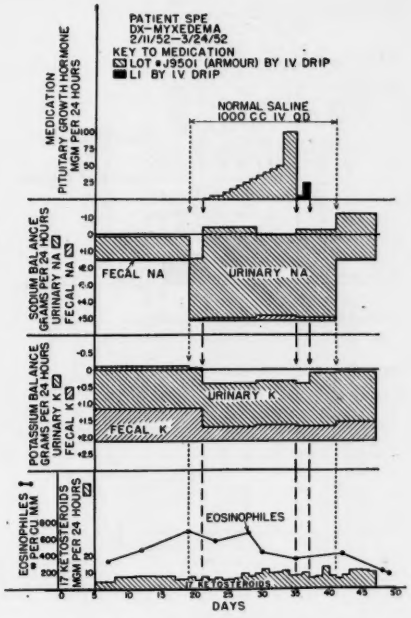


FIG. 3b. Lack of sodium retention or of significant change in eosinophils during "pituitary growth hormone" administration.

DISCUSSION

The observation of a positive growth effect with pituitary growth hormone preparations in 1 patient and a lack of growth effect or actual catabolic effect in 7 patients raises the following questions:

1. Is the 1 positive observation spurious?

2. If not, what accounts for the differential effects in the 1 as compared to the 7?

In view of simultaneous retention of all the constituents of protoplasm which were measured; of the "rebound" of nitrogen, potassium and phosphorus when the hormone was discontinued; of no sodium retention; of weight gain during treatment; and of weight loss during the period of post-

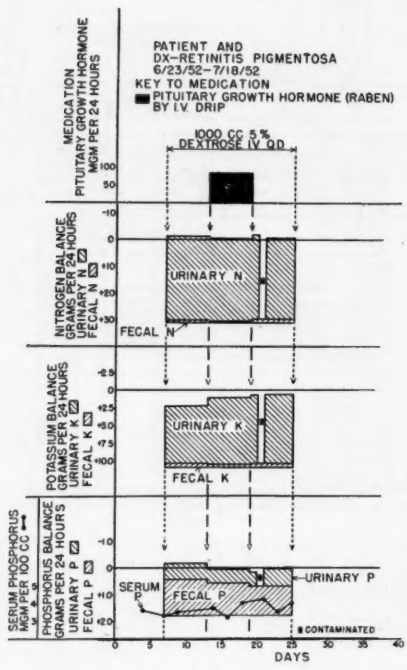


FIG. 4. Lack of consistent changes in constituents of protein tissue in a patient receiving "pituitary growth hormone" (Raben). No effect on circulating eosinophils or urinary 17-ketosteroids was observed.

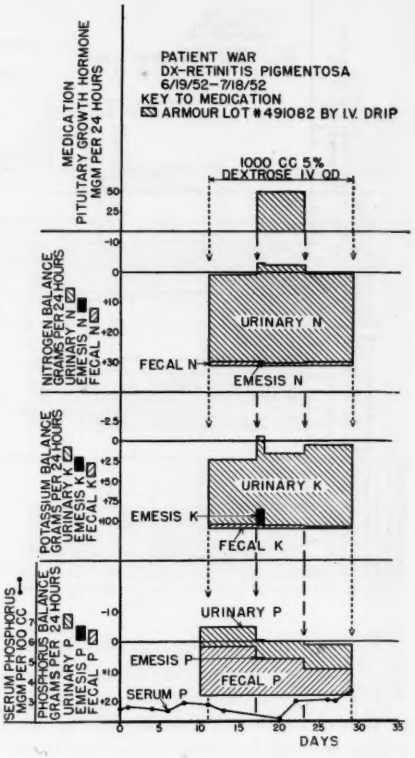


FIG. 5. Lack of nitrogen retention in patient receiving "pituitary growth hormone" (Armour, Lot #491082, contaminated with ACTH). A typical "ACTH type" fall in eosinophils and a rise in urinary 17-ketosteroids were observed.

hormone "rebound," it seems probable that the positive effect was real and not spurious. Why then the difference? The possibilities are several:

1. The nature of the patient (*i.e.*, lack of thyroid tissue).
2. The nature of the particular lot(s) of hormone.
3. The avenue of administration.

It may very well be that all three played a part. Whatever the answer, the following concepts seem tenable to us:

1. There *is* a pituitary growth hormone which makes humans grow (*cf.* acromegaly, gigantism, and pituitary dwarfism).
2. Portions of the earlier lots of growth hormone used by us (and others)

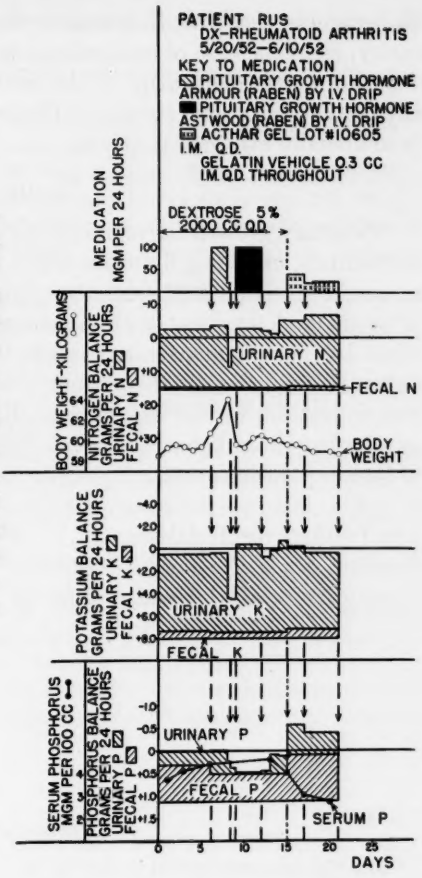


FIG. 6. Lack of definite protein anabolic effect from either of two growth hormone preparations ("pituitary growth hormone" Armour, Lot #491082; and Raben's). Both patients receiving the Raben material retained phosphorus. Calcium determinations, unfortunately, were not carried out. Eosinophil and 17-ketosteroid changes, marked fluid retention, and amelioration of arthritis in this patient during administration of "pituitary growth hormone" (Armour, Lot #491082) indicated its high ACTH content. Lack of potassium loss *may* have been referable to its pituitary growth hormone content. "Pituitary growth hormone" (Raben) produced no interpretable effect in the dosage used.

were denatured sufficiently to manifest, in the net, only nonspecific foreign protein effects. Presumably their ability to make rats grow speaks for the known toughness of this rodent.

3. To the best of our knowledge, no lot of thyrotropin-free pituitary growth hormone has ever been used. Since one may safely assume that these two functional elements are not a single chemical entity, all so-called "pure growth hormone preparations" are still very crude materials in a physiologic sense.

4. In view of the foregoing, it appears that the protein chemists have some hard work ahead.

5. When pure growth hormone is available, it will probably be non-

diabetogenic, *i.e.*, the diabetogenic factor will be found to be a separate entity, as in the case of contaminating thyrotropin.

6. For better delineation of the picture, it would seem desirable to carry out further metabolic studies in the immediate future with spontaneously or artificially athyroid patients.

SUMMARY

"Pituitary growth hormone preparations" have been administered to 8 individuals, including 3 normal adult males, 1 patient with panhypopituitarism, 2 patients with retinitis pigmentosa, 1 patient with rheumatoid arthritis, and 1 patient with myxedema. No unequivocal protein anabolic effect has been demonstrated except in the case of the patient with myxedema. It is not clear at the present time whether thyrotropin contamination was responsible for the lack of anabolic effect in the other patients studied, or whether the difference was referable to a variation in the composition of the preparations used.

The Institute for Metabolic Research of the Highland Alameda County Hospital, Oakland, California

LAURANCE W. KINSELL, M.D.
SHELDON MARGEN, M.D.*
JOHN W. PARTRIDGE, M.D.†
GEORGE D. MICHAELS, PH.D.
HARRY E. BALCH, M.D.
JOHN P. JAHN, M.D.
with the technical assistance of June Bilisoly, Marjorie Coelho, Eleanor Kipp, and Florence Olson

Acknowledgments

Grateful acknowledgment is made to Dr. Choh Hao Li, Department of Biochemistry, University of California; Dr. Edwin Hays and his associates, The Armour Laboratories, Chicago; and to Drs. Maurice Raben and E. B. Astwood, Pratt Diagnostic Clinic, Boston, for supplies of pituitary growth hormone.

The initial portion of this work was supported by grants from the Research Division of the Bureau of Medicine and Surgery of the United States Navy (BuMed No. 007046). More recent work has been supported by grants from the Armour Laboratories and from the Office of the Surgeon General, United States Army (Contract #DA–49–007–MD–109).

REFERENCES

1. YOUNG, F. G.: Growth and diabetes in normal animals treated with pituitary (anterior lobe) diabetogenic extract, *Biochem. J.* **39**: 515, 1945.

* Schering Clinical Research Fellow, 1948–1949; Damon Runyon Clinical Research Fellow, 1949–1951.

† Schering Clinical Research Fellow, 1950–1952.

2. *a.* Li, C. H., and Evans, H. M.: Isolation of pituitary growth hormone, *Science* **99**: 183, 1944.
   b. Li, C. H.: Sulfur amino acids in growth and adrenocorticotrophic hormones, *Fed. Proc.* **5**: 144, 1946.
3. *a.* Fishman, J. B.; Wilhelmi, A. E., and Russell, J. A.: A crystalline pituitary protein with high growth activity, *Science* **106**: 402, 1947.
   b. Wilhelmi, Alfred E.; Fishman, J. B., and Russell, J. A.: A new preparation of crystalline anterior pituitary growth hormone, *J. Biol. Chem.* **176**: 735, 1948.
4. Li, C. H., and Evans, H. M.: The biochemistry of pituitary growth hormone, *in* Recent Progress in Hormone Research, edited by G. Pincus. New York, Academic Press Inc., 1948, vol. 3, p. 3.
5. *a.* Michaels, G. D.; Margen, S.; Liebert, G., and Kinsell, L. W.: Studies in fat metabolism. I. The colorimetric determination of ketone bodies in biologic fluids, *J. Clin. Invest.* **30**: 1483, 1951.
   b. Michaels, G. D.; Anderson, C. T.; Margen, S., and Kinsell, L. W.: A method for the colorimetric determination of calcium and magnesium in small amounts of urine, stool and food, *J. Biol. Chem.* **180**: 175, 1949.
   c. Giragossintz, G. D.; Davidson, C., and Kirk, P. L.: The microdetermination of blood sugar by ceric sulphate titration, *Mikrochemie* **21**: 21, 1936.
   d. Kirk, P. L.: A one piece glass micro-Kjeldahl distillation apparatus, *Indust. & Engin. Chem.*, Analyt. Ed. **8**: 223, 1936.
   e. Fiske, C. H., and SubbaRow, Y.: The colorimetric determination of phosphorus, *J. Biol. Chem.* **66**: 375, 1925.
6. Olson, F.; Michaels, G.; Partridge, J. W.; Boling, L.; Margen, S., and Kinsell, L. W.: The use of formula diets administered via polyethylene tube or orally for constant intake (balance) studies, *J. Clin. Nutrition* **1**: 134, 1953.
7. Raben, M. S., and Westermeyer, V. W.: Differentiation of growth hormone from the pituitary factor which produces diabetes, *Proc. Soc. Exper. Biol. & Med.* **80**: 83, 1952.

Teaching Clinic

VALUE OF A THERAPEUTIC TRIAL WITH THYROID

THYROID substance has been widely used for many years. Certain associated hazards are well known. These include: overdosage, usually the consequence of inadequate supervision, resulting in undue strain on the circulation; the rare occurrence of actual hyperthyroidism following thyroid medication; and also depression of the function of the patient's own gland during the time that thyroid substance is administered. Johnston, Squires and Farquharson (1) have demonstrated, however, that in nearly all instances the thyroid gland recovers normal function within two to three weeks after the cessation of therapy.

Although there is never a question about the use of thyroid substance in obvious myxedema—in a dose which does not endanger the patient's circulation—there seems to be an increasing tendency to withhold thyroid from patients who do not have definite laboratory evidence of hypothyroidism, even though some clinical indications are present. The following case is presented in order to demonstrate that strict adherence to this rule will occasionally withhold beneficial treatment, and to show the value of a therapeutic trial of thyroid substance, especially in cases in which the underlying hypothyroidism is mild or dubious.

CASE HISTORY

The patient was a 36-year-old housewife whose chief complaints in November 1952 were lack of strength, and a tendency to gain weight easily. She had noted some enlargement of the thyroid since early childhood, but there had been no increase in size for many years. She reported being tired and "droopy" to a varying degree most of her life, even in childhood being considerably less active than her companions; also, she had always found it difficult to keep her weight within reasonable limits, and it had been necessary to curtail her caloric intake periodically. She had been raised in Iowa in an area in which goiters were common. After marriage at the age of 20 she had had a normal pregnancy, but there had been some difficulty in becoming pregnant a second time. This was accomplished several years later, however, after two years without contraceptives, and a second normal pregnancy resulted. Her two children were aged 16 and 4 years. She had always tended to be cold and preferred warm weather. A brief trial (one

week) of desiccated thyroid in the past had seemed to increase her appetite disproportionately, so she was advised to stop it and had never tried it again.

Her past history revealed an attack of poliomyelitis at the age of 24, which had involved principally the right calf. There had been fairly good recovery , although she was still bothered by low back pain radiating to the hips and with numbness of the right thigh, right calf and right foot. Consultants suggested that she had had an intervertebral disc protrusion which was not severe and which had probably subsided spontaneously. Menstrual periods were regular every twenty-six days, but lasted seven to eight days with profuse flow for six days.

Laboratory examination in November 1952 showed a basal metabolic rate of +16 per cent and a plasma cholesterol level of 245 mg. per 100 ml. Blood counts were normal.

On physical examination, she was 5 ft. 5½ in. in height and her weight was 169 pounds; B.P. was 128/76. The thyroid showed a slight diffuse, soft, symmetrical enlargement. It was concluded that there was not sufficient evidence for a diagnosis of hypothyroidism, and she was started on a reducing diet with the addition of Dexedrine. She felt somewhat better and lost 30 pounds in six months to a level of 139 pounds. At this point she experienced a spell of rather marked exhaustion, so the diet was stopped and in one month she regained 10 pounds. She then resumed her diet, but did not lose, and was troubled considerably by lack of strength and energy. She also complained of sensitivity to cold, slight dryness of the skin, brittleness of the nails, and a feeling of constant hunger. Menses were unchanged. There was a tendency to constipation.

The patient was examined again on July 22, 1953. At that time moderate obesity (151 pounds) was noted, and also a definite puffiness about the eyes. The heart was regular with a rate of 80, the B.P. was 120/80, and the thyroid was slightly and diffusely enlarged, soft and symmetrical, as before. There was some numbness over the maxillary division of the fifth nerve on the right side of the face and also some diminished sensation on the lateral aspect of the right thigh. The skin was slightly dry and of fine texture; the hair was of medium texture and also somewhat dry.

Laboratory examination showed: basal metabolic rate −5 per cent, plasma cholesterol level 197 mg. per 100 ml., serum protein-bound iodine level 5.6 micrograms per 100 ml., Hgb. 13.8 Gm. per 100 ml., and WBC 6,050 per cu. mm.

After consultation on August 18, 1953, it was decided to make a therapeutic trial of thyroid substance, because of the patient's suggestive symptoms and appearance, and in spite of the normal laboratory results. Accordingly, desiccated thyroid was started in a dose of .065 Gm. (1 grain) each morning.

After two weeks of treatment the patient reported that beginning on the second day she had felt greatly improved. Her general strength was better, there was less sensation of pressure in her neck, and she had noted an increased feeling of warmth. She stated that she felt better than ever in her life. She had lost 2 pounds; the pulse rate was 84, and B.P. 110/70. Thyroid therapy was continued. On September 14, 1953, her basal metabolic rate was +12 per cent and the plasma cholesterol level, 191 mg. per 100 ml. The patient stated that she now felt well. She was more active than usual, and recently had upholstered two chairs—a very unusual amount of activity. There had been no nervousness, palpitation or tremor from the thyroid medication and she felt warmer, her skin was not so dry, her color had improved and the thyroid gland itself seemed slightly smaller. One menstrual period had occurred on September 11, lasting four days with heavy flow for only one day, contrasting with the usual seven to eight days with heavy flow for six days. The numbness in her face had disappeared and the numbness in

her leg had diminished. The tendency to constipation was no longer present. On this date her weight had decreased another 3 pounds; the heart was regular with a rate of 90, and the B.P. was 120/70.

She then was given placebo tablets. On her next visit, fifteen days after starting the placebo medication, she reported that after three days she had begun to feel badly and now was about as she had been before starting thyroid. Symptoms which had returned were: exhaustion, sensitivity to cold, dryness and flaking of the skin, a sensation of fullness in the throat, constant hunger, increased numbness of the face and leg, and increased back pain. The constipation had not recurred. On examination, she had regained 5 pounds and was again moving slowly and obviously with some effort. The pulse was 75 and the B.P. 120/60.

Laboratory tests were then repeated, with the following results: basal metabolic rate −10 per cent, plasma cholesterol level 255 mg. per 100 ml., and serum protein-bound iodine level 5.7 micrograms per 100 ml.

She was advised to resume thyroid in a dose of .065 Gm. (1 grain) daily. When next seen ten days later, the improvement had reappeared but was somewhat masked by an acute head cold. Her skin and hair were less dry, and general strength and ambition were greater. Another menstrual period had occurred, lasting seven days; the flow was slightly heavier than with the previous one. She felt warmer, had less fullness in the throat and the numbness of her face had disappeared. The weight had dropped 2½ pounds; the pulse was 84 and the B.P. 120/70. Treatment with thyroid was continued.

It would appear that if thyroid had not been administered to this patient, because of the normal laboratory findings, the opportunity to help her considerably would have been missed.

As for the laboratory guides in hypothyroidism, the basal metabolism test is still the most widely used, and has the advantage of general availability and rapid reporting of results. Measurements of the level of plasma cholesterol also may be helpful; definite elevation is still considered an indication for the use of thyroid substance in many centers. The concentration of serum protein-bound iodine is a determination which is gradually becoming more available, and is particularly helpful in the diagnosis of hyperthyroidism. In hypothyroidism, however, strict interpretation will rule out some patients who might be helped by treatment with thyroid. The same can be said of the measurement of the thyroidal uptake of radioactive iodine.

It has been known for many years that in some women excessive menstrual flow may be controlled by the administration of desiccated thyroid, even when there are no other clinical signs of hypothyroidism and no laboratory evidence of that condition. The diminution in duration and degree of the menstrual flow in the patient reported here is an example.

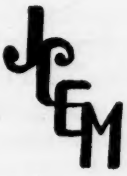
It seems logical to conclude that if clinical indications of hypothyroidism are found, or if there are suggestive symptoms present, a therapeutic trial of thyroid should be carried out, even if the laboratory

findings are normal. If necessary, this thyroid therapy may be interrupted with courses of placebos, a desirable maneuver from the point of view of scientific investigation.

ROBERTO F. ESCAMILLA, M.D.

655 Sutter Street,
San Francisco 2,
California

1. JOHNSTON, M. W.; SQUIRES, A. H., and FARQUHARSON, R. F.: The effect of prolonged administration of thyroid, *Ann. Int. Med.* **35**: 1008–1022 (Nov.) 1951.



Editorial

"CONDITIONING" VERSUS "PERMISSIVE" ACTIONS OF HORMONES

MUCH attention has been given of late to the so-called "conditioning" or "permissive" actions of hormones, especially in connection with research on stress and the adaptation syndrome. Some of the relevant discussions in the literature are rather complex and difficult to follow; hence, it may be instructive, by way of an introduction, to illustrate the underlying principle, with a simple diagram.

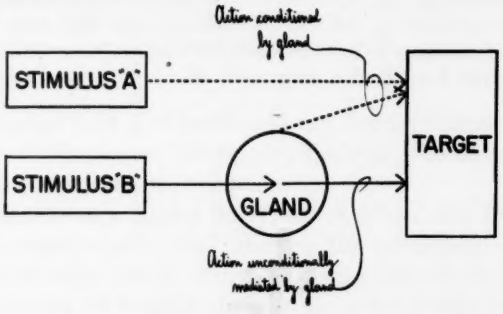


FIG. 1. Conditional and unconditional actions of stimuli, the effects of which depend upon an endocrine gland. [Reproduced from Selye and Collip (1) and Selye (12).]

Supposing a stimulus acts on a target organ in the presence, but not in the absence of an endocrine gland, two possibilities exist:

(A) the stimulus acts directly on the target organ, but only if the latter is maintained in a responsive condition by constant hormonal impulses, which it receives from the gland (interrupted lines),

(B) the stimulus has no direct effect upon the target, but merely induces the gland to release a hormone which, in turn, acts upon the target (solid lines).

In the course of our observations, these two mechanisms of action had first been clearly differentiated from each other on the basis of experiments concerned with the anterior pituitary. From these a general law, regulating hormone actions, was deduced in the following terms: "the fact that a certain stimulus is active in the presence, but inactive in the absence of the

pituitary does not necessarily prove that it acts by way of stimulating the output of a certain pituitary principle. It is equally possible that stimuli, usually influencing a pituitary-controlled tissue, are inactive after hypophysectomy only because of the atrophy of the tissue on which they should act. Thus, for instance, estrin may be unable to act on the atrophic gonad and adrenal cortex of an hypophysectomized animal, simply because the atrophic tissue is no longer able to respond. Similar considerations may be extended to the action of any stimulus affecting an endocrine-controlled tissue. Such stimuli may induce the endocrine to produce more hormones, or they may act directly upon the tissue, but only if this tissue is maintained in a responsive condition by the simultaneous hormonal stimulus, received from the endocrine in question" (1).[1]

At the time this statement was made, numerous experiments had been performed on hypophysectomized rats maintained in an essentially normal condition by continuous substitution therapy, with pituitary extracts. In these instances, the target organs were well maintained but there could be no stimulation of endogenous pituitary hormone production. Thus it was possible to establish for many stimuli, the effects of which depend upon the integrity of the pituitary, whether they act through one or the other of the pathways just outlined. Incidentally, it was only on the basis of such experiments that the mechanism through which stress affects the adrenal cortex could be clarified. We noted that stressors such as "formaldehyde, which caused marked adrenal hypertrophy in the normal, but not in the hypophysectomized animal, remained without effect, even if the adrenal cortex was prevented from undergoing atrophy by the administration of pituitary extract. The effect of such a drug on the adrenal appears to be an indirect one due to pituitary stimulation" (1).

Actually, these considerations apply to any physiologic response, and are by no means limited to hormone actions; however, unless a particularly important conditioning factor actually can be identified, the point hardly deserves special mention. If we stimulate the secretory nerves of the salivary glands and thus induce an increased production of saliva, it is customary to say that these nerves "cause salivary secretion." In the same sense, we commonly speak of adrenalin as "causing glycogenolysis" and so forth. In all such instances, however, it is silently understood that nerves cannot produce secretion, and adrenalin cannot cause glycogenolysis, directly and unconditionally, irrespective of all other conditions prevailing in the organism.

Indeed, it would be virtually impossible to discuss any subject of medical

[1] It should be mentioned, incidentally, that it is immaterial whether we say that the hormone conditions the effect of the nonhormonal stimulus, or vice versa, since synergism between both factors is necessary to obtain an optimal response.

research if we could not take it for granted that when we say "the stimulus A produces the change B," this is true only under conditions which permit the reaction. Although most readers will consider this to be self-evident, it has been the source of many debates in the field of stress-research, perhaps because the action of adaptive hormones (*e.g.*, corticoids, ACTH, STH) and the direct effects of stress itself, are singularly subject to modification by such "conditioning factors."

Let us merely mention four pertinent examples which have been studied in our Institute (for references *cf.*: 2, 3, 4, 5):

1. DCA causes nephrosclerosis in rats kept on a diet with a normal sodium content. However, this nephrosclerotic action is greatly exaggerated by an excessive sodium intake, whereas it is virtually abolished by sodium deprivation. From this we have concluded that sodium is a "conditioning factor" of this DCA action. One might formulate this alternatively by saying that DCA conditions these effects of sodium.

2. Traumatic shock produces hyperglycemia in the intact rat, but hypoglycemia in the adrenalectomized rat. If an adrenalectomized rat is maintained on threshold doses of adrenocortical extracts (which in themselves cause no hyperglycemia) it can again respond to surgical shock normally, by a marked rise in blood sugar. Apparently the stress of traumatic injury does not raise the blood sugar level merely through the excessive production of glucocorticoids, nor do the glucocorticoids exert their maximal hyperglycemic action by themselves. We may conclude that the metabolic changes incident to stress produce favorable conditions for the manifestation of the hyperglycemic effect of glucocorticoids.

3. The "endocrine kidney operation" causes hypertension in the intact but not in the adrenalectomized rat. If an adrenalectomized rat is maintained on threshold doses of adrenocortical extracts (which in themselves cause no hypertension), it again exhibits a rise in blood-pressure as a result of the endocrine kidney.

4. Glucocorticoids, such as cortisone, elicit thymus involution both in the intact and in the adrenalectomized rat. On the other hand, stress causes thymus involution—concurrently with manifestations of increased glucocorticoid production—in the intact rat, but fails to affect the thymus of an adrenalectomized animal. Yet even the thymus involution caused by glucocorticoids is not exclusively the result of these hormones alone. If adrenalectomized rats are exposed to stress while receiving threshold doses of glucocorticoids (amounts which in themselves cause little or no thymus involution) they exhibit a pronounced disintegration of thymus tissue during the ensuing alarm reaction. Apparently here again the metabolic changes induced by the general adaptation syndrome, although unable to cause thymus involution by themselves, sensitize or "condition" the organism to

the development of this change under the influence of glucocorticoids.

Many additional examples of such conditioning actions have subsequently been reported from various other laboratories. For instance, Whitney and Bennett (6) found that, in rats, the catabolic effect of ACTH can be inhibited by a diet rich in KCl. Indeed, even the diabetes-enhancing action of ACTH is similarly suppressed by an excessive potassium intake (7).

Estradiol suppresses hair growth in intact, but not in adrenalectomized rats. Large doses of adrenocortical extract inhibit hair growth, both in the intact and in the adrenalectomized rat. Yet, it would be false to conclude that the estradiol acts exclusively by stimulating the endogenous production of corticoids. This is shown by the fact that adrenalectomized rats given threshold amounts of the extract (in themselves ineffective) can exhibit suppression of hair growth under the influence of concurrently administered estradiol. From this, Ingle (8) concluded that the latter hormone suppresses hair growth, but only on condition that there is an adequate blood corticoid level to permit this effect.

On the basis of these and similar observations, one group of investigators (8, 9, 10) formulated the hypothesis that "the adrenal cortex plays a 'permissive' rôle during stress, being necessary but not responsible for certain metabolic and other changes" (11).

The term "permissive" action implies that the factor so designated is entirely inert in itself, although it allows another stimulus to act. The term "conditioning" has no such connotations. This impresses us as an advantage, especially in the field of stress-research, because many of the effects of adaptive hormones (*e.g.*, corticoids) are largely dependent upon concurrent metabolic changes induced by stress; yet most of them are demonstrable, even in the absence of stress, if larger doses of such hormones are given.

Furthermore, allegedly, the presence or absence of a permissive factor can only allow or disallow a reaction, but is unable to vary its intensity. To use an analogy, one might compare the production of light by an electric lamp to the biologic action and the switch to the "permissive factor." A simple switch cannot produce light, nor regulate the degree of its intensity; but unless it is turned on, the lamp will not function. A switch can only permit or disallow the production of light.

The possibility cannot be refuted that such "permissive actions" may play a rôle in stress responses, but we would be hard-pressed to cite a clear-cut example. On the other hand, there are many hormonal actions, the intensity of which depends just as much upon the presence of (hormonal or non-hormonal) conditioning factors, as upon the blood level of the apparently responsible hormone itself. The importance of such conditioning influence is particularly striking in the regulation of stress reactions because, in the final analysis, they are the factors which can actually determine

whether exposure to a stressor will be met by a physiologic adaptation syndrome or by a "disease of adaptation." Furthermore, in the latter instance, these conditioning factors can even determine the selective breakdown of one or the other organ. We are led to believe that differences in predisposition, due to such factors, may explain why the same kind of stressor can cause diverse types of "diseases of adaptation" in different individuals.

As long as these facts are kept in mind, we consider it proper to designate a manifestation of stress as "due to hypercorticoidism," whether it results from an actual increase in corticoid production or from a selective sensitization of target organs to these hormones, through some conditioning factors. This manner of expression is in keeping with common English usage. For instance, we speak of a room as being "overheated," not only when more heat is produced by the furnace, but also when an increase in the outside temperature or a better heat insulation lessens heating requirements. In either case, it is correct to say that "the heating system is overworking."

It is hoped that these considerations will help to clarify and delimit the concepts of "conditioning factors," "permissive factors" and "hormone-overdosage manifestations," which are so frequently, and sometimes confusingly, handled in the current literature.

HANS SELYE, M.D.

Institute of Experimental Medicine and Surgery,
Université de Montréal,
Montreal, Canada

REFERENCES

1. SELYE, H., and COLLIP, J. B.: Fundamental factors in the interpretation of stimuli influencing endocrine glands, *Endocrinology* **20**: 667, 1936.
2. SELYE, H.: Stress. The Physiology and Pathology of Exposure to Systemic Stress. Montreal, Canada, Acta Inc., Med. Publ., 1950.
3. SELYE, H.: First Annual Report on Stress. Montreal, Canada, Acta Inc., Med. Publ., 1951.
4. SELYE, H., and HORAVA, A.: Second Annual Report on Stress, Montreal, Canada, Acta Inc., Med. Publ., 1952.
5. SELYE, H., and HORAVA, A.: Third Annual Report on Stress, Montreal, Canada, Acta Inc., Med. Publ., 1953.
6. WHITNEY, J. E., and BENNETT, L. L.: Inhibition of the catabolic effect of adrenocorticotropic hormone (ACTH) in rats by a diet high in potassium chloride, *Endocrinology* **50**: 657, 1952.
7. GLAFKIDES, C. M.; BENNETT, L. L., and GEORGE, R.: Inhibition of the diabetes enhancing effect of ACTH by a diet high in potassium chloride, *Endocrinology* **50**: 684, 1952.
8. INGLE, D. J.: Hormones and metabolism; parameters of metabolic problems, *in* Recent Progress in Hormone Research. New York, N. Y., Academic Press Inc., 1951, vol. 6, p. 159.

9. INGLE, D. J., and BAKER, B. L.: A consideration of the relationship of experimentally produced and naturally occurring pathologic changes in the rat to the adaptation diseases, *in* Recent Progress in Hormone Research. New York, N. Y., Academic Press Inc., 1953, vol. 8, p. 143.
10. BURNS, T. W.; ENGEL, F. L.; VIAU, A.; SCOTT, J. L., JR.; HOLLINGSWORTH, D. R., and WERK, E.: Studies on the interdependent effects of stress and the adrenal cortex on carbohydrate metabolism in man, *J. Clin. Invest.* **32**: 781, 1953.
11. ENGEL, F. L.: On the nature of the interdependence of the adrenal cortex, nonspecific stress and nutrition in the regulation of nitrogen metabolism, *Endocrinology* **50**: 462, 1952.
12. SELYE, H.: Textbook of Endocrinology. Montreal, Canada, Acta Endocrinologica; ed. 1, 1947; ed. 2, 1949.

Questions and Answers

(Questions submitted at the 1952 Postgraduate Assembly of the Endocrine Society)

Answers by Dr. C. L. Buxton, Columbia-Presbyterian Medical Center, New York, N. Y.

QUESTION: How do you explain the treatment of psychic amenorrhea with Prostigmin and Prostigmin-like drugs?

ANSWER: Prostigmin and Prostigmin-like drugs have been used in cases of amenorrhea as a pregnancy test. Following administration of one of these substances, if the patient is not pregnant, uterine bleeding is supposed to ensue within twenty-four hours, but in the presence of pregnancy there is no menstruation. The use of this drug in the manner described is based on the work of Reynolds (1) who found an increase in the acetylcholine content of the uteri of spayed rabbits given estrogen. It was thought that this accounted for the uterine hyperemia associated with estrus and hence might be concerned with menstrual bleeding. Prostigmin produces an acetylcholine effect by inhibiting its destruction by the enzyme cholinesterase, and therefore the Prostigmin effect in the so-called pregnancy test has been interpreted as the result of a direct parasympathetic stimulation of the uterus (2).

1. REYNOLDS, S. R. M.: Acetylcholine content of uteri before and after administration of oestrin to ovariectomized rabbits. *J. Physiol.* **95**: 258. 1939.
2. FLUHMANN, C. F.: Diseases of the female reproductive system. *Annual Review of Medicine* 1952, vol. 4, p. 206.

QUESTION: What is your opinion as to the best method of treatment of premenstrual tension?

ANSWER: The present generally accepted theory as to the etiology of premenstrual tension is about as follows: Steroid concentration during the latter half of the menstrual cycle results in sodium ion retention, which in turn results in general body fluid accumulation, including a certain amount of edema throughout the nervous system. This gives rise to the many symptoms of nervous irritability and emotional instability that characterize the syndrome which has come to be known as premenstrual tension.

The most satisfactory treatment of this condition, therefore, is simple dehydration during the latter half of the menstrual cycle. This is accomplished by a salt-poor regimen and the administration of from 3 to 5 grams of ammonium chloride per day. If the latter produces nausea it may be supplied in enteric coated capsules, or the patient may also be given small doses of Dramamine.

Answers by Dr. Willard M. Allen, Washington Univ. School of Medicine, St. Louis, Mo.

QUESTION: What is the evidence for increased adrenal activity producing increased facial hair at the time of the climacteric? Urinary 17-ketosteroid levels do not usually indicate this to be so.

ANSWER: There is virtually no laboratory evidence to support the idea that increased adrenal activity is responsible for the moderate virilism which is seen in some women following the menopause. Failure to find significant increases in the urinary 17-ketosteroids does not, of course, eliminate the possibility that an increased level of androgen causes the virilism. The administration of testosterone in doses of 100 mg. per week will induce virilism in some women in two or three months. This dose will not materially increase the excretion of urinary 17-ketosteroids. Similarly, patients with arrhenoblastomas or Leydig-cell tumors of the ovary may be markedly virilized without much elevation of the urinary 17-ketosteroids. It seems possible, therefore, that the virilism of the climacteric may be due to the production of androgens, either by the adrenal or ovary and this production is not reflected in the urinary 17-ketosteroids as determined by the usual tests.

QUESTION: Do you find any difference in the course of pregnancy in a recent diabetic compared with that in a long-term diabetic?

ANSWER: It is fairly common knowledge among obstetricians that those patients who have had diabetes for many years (in general, those who have had diabetes since childhood or adolescence) are more difficult to manage during pregnancy. They seem to be more subject to acidosis and the risk to the fetus is greater than in older patients who may have acquired diabetes later in life. This impression may be erroneous. The statistics regarding diabetes and pregnancy do not, as a rule, adequately separate the results obtained in patients with long-standing and severe diabetes from those obtained in patients with later development of the diabetes.

QUESTION: What is the rationale of giving thiamine-chloride (or B-complex) with estrogen intramuscularly? Does it potentiate the estrogen?

ANSWER: Thiamine-chloride (or B-complex) may play an important role in the normal inactivation of estrogens by the liver. Studies in vitamin-B deficient animals indicate that such deficiency may interfere with the enzymic destruction of estrogens in the liver. Similarly in liver disease, such as cirrhosis, gynecomastia may appear in males, probably because of inadequate destruction of estrogens. These observations provide no real indication for the combined use of estrogen and vitamin-B complex clinically, except in presumed liver disease or vitamin-B deficiency. There is virtually no indication that vitamin-B is anything more than a harmless and possibly beneficial adjunct to estrogen therapy.

QUESTION: Does progesterone have any effect on the vasomotor instability of the climacteric?

ANSWER: There is no evidence that progesterone has any beneficial effect on the vasomotory instability of the climacteric.

QUESTION: Please discuss the value and method of culdoscopy. May laparotomy ever be avoided by using this diagnostic method?

ANSWER: Culdoscopy is a procedure in which a culdoscope is passed through the posterior vaginal fornix into the peritoneal cavity. The procedure can be carried out under local anesthesia and is not accompanied by much pain or risk. Culdoscopy has not found wide

acceptance by gynecologists, since in most situations a decision is readily made regarding the need for laparotomy without this added diagnostic procedure. It may be indicated in some cases of ectopic pregnancy but in most cases the more simple aspiration of the cul-de-sac with syringe and needle will provide the information necessary. In cases of endometriosis, culdoscopy should seldom be performed, because the sigmoid is frequently attached to the posterior aspect of the uterus. The chief value of culdoscopy will be found in situations in which visualization of the ovaries is desirable. The culdoscope should be helpful in appraising the nature of small ovarian cysts, and in functional disturbances or sterility when inspection of the ovaries may help in the diagnosis and treatment.

Answer by Dr. E. Perry McCullagh, Cleveland Clinic, Cleveland, Ohio

QUESTION: What is the approximate incidence of postoperative exophthalmos in Graves' disease?

ANSWER: No thoroughly satisfactory answer can be given to the question of the incidence of postoperative exophthalmos in Graves' disease, because an insufficient number of measurements have been made over a prolonged period of time before and after thyroidectomy. The question might be taken to imply that exophthalmos occurring postoperatively is due in whole or in part to the effects of surgery. It would be well for all those considering the problem to realize clearly that exophthalmos may become extremely severe postoperatively while the metabolism is rising to levels decidedly above normal; moreover, as noted in the older literature, exophthalmos may become so severe as to cause the loss of both eyes in cases in which no thyroid surgery has been performed.

McCullagh (1) showed that some degree of increase in proptosis occurred in approximately one half of a small group of patients followed postoperatively for six to thirty-six months. Dobyns (2) obtained repeated careful measurements of the degree of proptosis in 233 patients, for the most part over a period of not more than two months. During this period evidences of hyperthyroidism were disappearing during treatment, but true prominence of the eyes increased 1.25 mm. or more in 65.3 per cent of the patients subjected to thyroidectomy. Soley (3) showed that an increase of 1.5 mm. took place in 40 per cent of the patients whom he followed after thyroidectomy.

It is evident that during similar periods of time exophthalmos disappears in many patients. Whether this is spontaneous or in some way connected with the disappearance of the hyperthyroidism per se is unknown. Mild degrees of exophthalmos, of the order of those mentioned, are usually of little clinical consequence. Few estimations are available as to the actual frequency of severe exophthalmos postoperatively. It is certain that progressive exophthalmos or so-called malignant exophthalmos is of relatively rare occurrence. Hugh Ryan (4) reviewed the problem in 1,001 patients following thyroidectomy. Adequate information was received from 584. Among them there were 3 cases of what he classed as thyrotropic exophthalmos of mild degree, and no gross cases were found. By thyrotropic exophthalmos he meant the type associated with proptosis, swelling of the lids, stasis edema, edema of the conjunctiva and orbital contents, and weakness of the extraocular muscles. This type of exophthalmos, if severe, sometimes leads to corneal ulceration and ophthalmitis. In such cases, "thyrotropic" has an etiologic significance which is unacceptable to many workers.

Poppen (5) states that orbital decompression for exophthalmos in patients successfully treated for hyperthyroidism is found desirable in about 1 patient in 1,000. This apparently is close to the experience of others.

As to the percentage of spontaneous remission of eye signs in Graves' disease, no adequate answer seems to be available, since patients who have Graves' disease and come to the attention of a physician almost invariably receive therapy which may in itself influence the progress of the exophthalmos.

1. McCullagh, E. P.; Ruedemann, A. D., and Gardner, W. J.: Exophthalmos of Graves' disease following pituitary irradiation, orbital decompression and electrocautery to the pituitary gland, *Tr. Am. A. Study Goiter* 1942–1946, pp. 15–32.
2. Dobyns, B. M.: Present concepts of the pathologic physiology of exophthalmos, *J. Clin. Endocrinol.* **10:** 1202–1230 (Oct.) 1950. *Tr. Am. Goiter A.* 1950, pp. 275–303.
3. Soley, M. H.: Exophthalmos in patients with various types of goiter, *Arch. Int. Med.* **70:** 206–220, 1942.
4. Ryan, Hugh: Thyroidectomy and thyrotropic exophthalmos (exophthalmic ophthalmoplegia): a review of 1,001 thyroidectomies, *Brit. J. Ophthalmol.* **33:** 769, 1948.
5. Poppen, James: Intractable exophthalmos in thyroid disease, *Postgrad. Med.* **14:** 130, 1953.

Answers by Laurance W. Kinsell, Highland Alameda County Hospital, Oakland, California

QUESTION: Since Cushing's disease includes cortisone production by the adrenal, would this not inhibit the production of ACTH and intermedin by the pituitary? Therefore, does it not account for the pigmentation of pregnancy?

ANSWER: It is probable that the pigmentation which occurs in pregnancy, in Addison's disease, and in some individuals receiving large amounts of ACTH, is referable to the effects of "intermedin-like substances."

QUESTION: What evidence is there that intermedin causes pigmentation in human beings?

ANSWER: In many patients receiving large amounts of ACTH, pigmentation develops. This is true, even in the case of highly purified ACTH preparations. It is still not determined whether intermedin is a chemical part of the ACTH entity in such preparations or whether it is yet to be separated.

QUESTION: Is cortisone indicated in pregnancy complicated by chronic exfoliative dermatitis?

ANSWER: In my opinion neither cortisone nor ACTH should be administered to a pregnant woman unless a condition is present which seriously endangers the health or the life of the woman. Under such circumstances, the dosage of the hormones should be kept at the minimal effective level, in order to minimize the possibility of abnormalities in the developing fetus.

QUESTION: Did Young's dogs, made diabetic by the administration of growth hormone, show acromegaly? Is it possible that some cases of diabetes are due to growth hormone, not involving acromegaly?

ANSWER: Acromegaly per se, to the best of my knowledge, has never been recognized in experimental animals, although significant growth stimulation has occurred in animals in which glycosuria and hyperglycemia developed during treatment with growth hormone. At the present time, one can only wonder whether growth hormone (or a diabetogenic factor intimately associated with growth hormone) is responsible for some forms of human diabetes. It is my very strong opinion that this is true.

QUESTION: To what may be attributed the diabetes which appears in the mother three years after the birth of a large baby?

ANSWER: One might postulate that in a woman in whom diabetes develops subsequent to the birth of a large baby, a pre-diabetic state was present at the time of the pregnancy. One might further postulate that the increased production of growth hormone during pregnancy was responsible both for the large baby and, in a measure, for the development of the diabetes.

QUESTION: Is there not an orally active anterior pituitary product available now?

ANSWER: There is no orally active anterior pituitary product which has any place in clinical medicine at the present time.

QUESTION: Is any treatment of value in vitiligo?

ANSWER: To the best of my knowledge, there is no treatment of value in patients with vitiligo.

HENRY S. GUTERMAN, M.D.

IN MEMORIAM

Born, October 20, 1915, in Worcester, Massachusetts.
Died, August 6, 1953, in Chicago, Illinois.

By those who knew him only through his scientific writings, Dr. Guterman will be best remembered for his fundamental contributions to the knowledge of sex endocrinology, particularly with respect to the functions and metabolism of progesterone.

His research career began in 1942, when he became a Research Fellow in the Department of Metabolic and Endocrine Research, of the Medical Research Institute of Michael Reese Hospital, Chicago. The present writer was then the director of the department. At that time Dr. Guterman was only two years beyond his graduation (cum laude) from the Washington University School of Medicine. He had spent the intervening two years in a clinical internship at Michael Reese Hospital, a circumstance which was perhaps partly responsible for his continuing interest in the application of basic science to clinical medicine.

He was productive from the start, and became successively a Research Associate (1944–46), and Assistant Director of the department (1946–53). In 1953 he achieved the status of a department head, when he became the Director of the Department for Research in Human Reproduction. Throughout the eleven years of his active scientific career he published some twenty-five original scientific contributions, most of them on the subject of his primary interest. His contributions and views are summarized in the recent review articles:

The Physiologic Basis for Clinical Application of Progesterone, *J. Clin. Endocrinol.* **10:** 641–665, 1950.

On the Significance of the Chemical Estimation of Compounds Related to Progesterone, *in* Ciba Foundation Colloquia on Endocrinology, edited by G. E. W. Wolstenholme. London, J. & A. Churchill, Ltd.; Philadelphia, The Blakiston Co., 1952, vol. 2, pp. 23–27.

On Possible Relationship Between the Metabolic Breakdown of Progesterone and its Biologic Activity, *Ibid.*, pp. 366–374.

To those who knew Dr. Guterman as a man and friend, his passing is a great personal loss. Though zealous in his work, he was self-critical to a fault; nor did he allow his strong, creative drive to dull his natural kindness and consideration of others. No self-seeker or laboratory politician, no egomaniac or actor, his ambitions were directed at the legitimate goals of the true scientist—to obtain and to wield the tools and the freedom to uncover

the facts in his chosen field. Uncomplaining and without self-pity, although for years he faced the certain knowledge that his days were numbered because of congenitally polycystic kidneys, he made the most of his allotted time. His friends will miss him and Endocrinology will be the poorer for his going.

SAMUEL SOSKIN, M.D.

405 North Bedford Drive,
Beverly Hills, California

SAMUEL L. SIEGLER, M.D. (F.A.C.S.)

November 12, 1894—September 15, 1953

Dr. Siegler was graduated from Fordham University Medical School in 1918. At the time of his death in Brooklyn, N. Y. he was Director of Obstetrics and Gynecology, Unity Hospital; Senior Attending Gynecologist and Obstetrician, Brooklyn Women's Hospital; Assistant Gynecologist and Obstetrician, Greenpoint Hospital; and Consultant in Obstetrics and Gynecology, Rockaway Beach Hospital.

He was a prominent member of many scientific and medical societies (including the Endocrine Society), and presented and published some forty papers relating to sterility, gynecology and obstetrics during the period 1928–1952.

He produced two motion pictures, approved by the American College of Surgeons and by the American Medical Association, namely: "Studies in Ovulation and Pregnant Mares' Serum" in sound and color; and "Sterility. Its Causes. Investigation and Treatment," translated into Spanish and Portuguese by the Inter-American Cultural Relations Committee of the United States State Department.

In 1945 he received the Lasker Award for his text book on "Fertility in Women."

The Endocrine Society

THE 1954 ANNUAL MEETING

The Thirty-sixth Annual Meeting of The Endocrine Society will be held in the Sir Francis Drake Hotel, San Francisco, California, Thursday, Friday and Saturday, June 17–18–19, 1954.

Dr. Roberto F. Escamilla, 655 Sutter Street, San Francisco, California, is in charge of the local arrangements for the meeting.

All Scientific Sessions will be held in the Sir Francis Drake Hotel. The rooms in which each session will be held will be announced in the program and on the hotel bulletin board. The annual dinner is scheduled for Friday, June 18, at 7:30 P.M., preceded by cocktails at 6:30 P.M.

Hotel reservations may be made through the San Francisco Convention and Visitors' Bureau, Room 300, Civic Auditorium, San Francisco, California. They should be accompanied by the official AMA application form which appears during December of 1953 in JAMA.

Arrangements have been made for members of this society who do not belong to the AMA to be assigned rooms during the days of the meeting of the Endocrine Society. Applications from nonmembers of the AMA should specify dates of arrival and departure and be accompanied by a deposit of $10.00 per room.

Confirmations will not be sent until after February 1, 1954, but *applications should be made promptly* in order to insure the reservation.

1954 AWARD AND FELLOWSHIPS

Awards and Fellowships presented by The Endocrine Society carry no obligation by the recipient to the Society or to the donors.

Fellowships

Society Fellowships are designed to assist men or women of exceptional promise in furthering their educational training and advancement toward a scientific career in endocrinology. Fellowships may be awarded to an individual who possesses the Ph.D. or M.D. degree or to a candidate for either of these degrees. The stipend, which will not exceed $5,000 may be divided into two Fellowships in varying amounts, in accordance with the qualifications of the appointee. The Committee will, in reviewing the proposed program of study, consider the amount of time which the Fellow intends to spend in course work and/or teaching. He must present evidence of scientific ability as attested by studies completed or in progress and/or the recommendation of responsible

individuals. He must submit a program of proposed study, indicate one or more institutions where the proposed program will be followed, and submit statements of approval from the investigators with whom he proposes to conduct his research. He must serve full time if awarded a Fellowship. A small amount of time (10 to 15 per cent) may be allotted for course work or for participation in teaching, the latter purely on a voluntary basis.

THE AYERST, McKENNA AND HARRISON FELLOWSHIP

The Ayerst, McKenna and Harrison Fellowship was first awarded in 1947 to Dr. Samuel Dvoskin and in 1948 to Dr. Ernest M. Brown, Jr. Dr. Brown was re-elected in 1949. The Fellowship in 1950 was awarded to Dr. Lawrence E. Shulman and in 1952 to Dr. John C. Laidlaw. In 1954 it will be in the amount of $5,000.

THE SCHERING FELLOWSHIP IN ENDOCRINOLOGY

This Fellowship will not be awarded in 1954 in order that it may accumulate toward a $5,000 Fellowship to be awarded in 1955.

Award

THE CIBA AWARD

The Ciba Award, to recognize the meritorious accomplishment of an investigator, not more than thirty-five years of age, in the field of clinical or preclinical endocrinology, was established in 1942, but no recipient was selected in 1942 or 1943. In 1944 the Award was presented to Dr. E. B. Astwood; in 1945 to Dr. Jane A. Russell; in 1946 to Dr. Martin M. Hoffman; in 1947 to Dr. Choh Hao Li; in 1948 to Dr. Carl Heller; in 1949 to Dr. George Sayers; in 1950 to Dr. Oscar M. Hechter; in 1951 to Dr. Albert Segaloff. Effective in 1952, the Award was increased from $1,200 to $1,800 and the recipient was Dr. Seymour Lieberman; in 1953 the Award was presented to Drs. Sidney Roberts and Clara Szego. If within twenty-four months of the date of the Award, the recipient should choose to use it toward further study in a laboratory other than that in which he is at present working, it will be increased to $2,500.

Nominations

Each member has the privilege of making one nomination for each Fellowship or Award. A nomination should be accompanied by a statement of the importance of the nominee's contributions to, or interest in, endo-

crinology and by a bibliography of the nominee's most important publications, with reprints if possible. The nominations should be made on special application forms which may be obtained from the Secretary, Dr. Henry H. Turner, 1200 North Walker Street, Oklahoma City, Oklahoma, and returned to him not later than *March 1, 1954.*

The American Goiter Association

THE 1954 ANNUAL MEETING

The annual meeting will be held at the Somerset Hotel, Boston, Massachusetts, April 29, 30 and May 1, 1954. It is suggested that you make your hotel reservations by writing Mr. Harry Hoghn, Executive Assistant Manager, The Somerset, 400 Commonwealth Avenue, Boston 15, Massachusetts.

JOHN C. MCCLINTOCK, M.D.,
Corresponding and Recording Secretary

VAN METER PRIZE AWARD FOR 1954

The American Goiter Association again offers the Van Meter Prize Award of Three Hundred Dollars and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The award will be made at the annual meeting of the Association which will be held in Boston, Massachusetts, April 29, 30 and May 1, 1954, providing essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations; should not exceed three thousand words in length; must be presented in English, and a typewritten double-spaced copy in duplicate sent to the Corresponding Secretary, Dr. John C. McClintock, 149½ Washington Avenue, Albany 10, New York, not later than *January 15, 1954.* The committee, who will review the manuscripts, is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for the presentation of the Prize Award Essay by the author, if it is possible for him to attend. The essay will be published in the annual Transactions of the Association.

AWARD OF MERIT FOR 1954

TO ALL MEMBERS OF THE AMERICAN GOITER ASSOCIATION

An anonymous gift of $1,000 to be awarded each year for three years has been accepted by the Executive Council of The American Goiter Association. The terms of the gift specify that this sum shall be given to a member of the Association under 45 years of age who has made the most important contributions to the knowledge and understanding of thyroid disease or the treatment of thyroid disease.

Candidates for this award are to be nominated by members of the Association. When making a nomination, complete details of the nominee's present and past positions and training must be submitted. A complete bibliography of the nominee's publications is required. A full explanation of the reasons for nominating the candidate must be given.

The nominations submitted are to be reviewed by an anonymous committee appointed by the president. The chairman of this committee will present the deliberations and decisions of said committee to the Executive Council in advance of the annual meeting.

The award is to be called The American Goiter Association Award of Merit and shall be presented at the annual banquet.

You are requested to send two copies of your nominations to this secretary, making certain the information required by the deed of gift is included. All nominations must be received not later than *February 1, 1954.*

JOHN C. MCCLINTOCK, M.D.
Recording and Corresponding Secretary

149½ Washington Avenue,
Albany 10, N. Y.